ANNALS
OF
OTOLOGY, RHINOLOGY
AND
LARYNGOLOGY

VOL. 69 JUNE, 1960 No. 2

XXVII

COMBINING ANTIBIOTIC WITH ANTIGEN THERAPY IN CASES OF T.O.E. (YEAST AND FUNGUS) ALLERGY

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Fifty cases of T.O.E. (Trichophyton, Oidiomycetes and Epidermophyton) allergy encountered in ear, nose and throat practice were treated successfully using the Titration Hyposensitization Method outlined by Rinkel[1] and Brown.[2] There was, however, in addition, a small group of patients who either got no help or actually got worse with the therapy.

Since the development of the yeast antibiotic, Nystatin (Mycostatin - Squibb), and the fungus antibiotic, Griseofulvin (Grifulvin - Schering and Fulvicin - McNeill), it seemed expedient to employ them as an adjunct to other therapy in these problem cases. It was hoped that by curing the chronic focus of infection, the allergy to the fungus or mold or its by-products ("id" reaction) could thereby be eliminated.

Brown has clearly outlined the management of T.O.E. cases and the importance of dietary restrictions to avoid T.O.E. or yeast food contacts. Nothing need be added to his outline of therapy. A few additional factors should be now added, however, to the previous diet list of T.O.E. contacts which he and I worked out.

Read before the Annual Meeting of the Gulf Coast Allergy Study Group at Houston, Texas, on February 6, 1960.

The first thing to be stated is that any food kept over more than a few days can offend: especially butter, ham, liver, salad oils, dried foods, nuts and fruits, syrups, jams, jellies and preserves. The second principle to be added is that food from animal source can cause symptoms where the animal has been constantly fed antibiotics in the food, either as a growth factor or to combat epidemic animal infections. A spot check of wholesale feed companies in Houston showed that almost all commercial livestock and poultry feeds contain antibiotics: either Terramycin, Aureomycin, Streptomycin, Penicillin or Bacitracin, singly or often in combination. Only one company could be found which could supply domestic animal feed without antibiotics. Quantities of antibiotics added varied from 5 to 250 grams per ton. If less than 50 grams per ton is used, it is not legally necessary in this State to make a notation on the label.

The six cases to be reported were treated with Nystatin or Griseofulvin or both as part of the over-all therapy as will be detailed shortly. No attempt was made to isolate either yeast or fungus organisms from local lesions. The diagnosis was made primarily by the positive T.O.E. titration intradermal tests and the presence of local lesions presumed to be associated with this sensitivity or "id" reaction. Possibly this was not a very scientific approach, but the purpose of using the antibiotics was to see if they would help solve these particular problem cases.

Hazen[6] in his monograph describing the discovery and therapy of Nystatin, classifies it as an antifungal antibiotic, especially effective against Candida Albicans or Monilia. It is derived from a mold known as Streptomyces Noursei. It is recommended for treatment of monilia infections by both systemic and/or local use. For systemic use it comes in tablets of 500,000 units and a pediatric suspension of 100,000 units per cc. Recommended dosage is three to four times daily for from a few days to a few weeks depending on response. For local use it comes as ointment, vaginal suppositories and dusting powders. The trade name is Mycostatin (Squibb). It is of very low toxicity. Side effects and adverse reactions are no problem.

Blank and co-workers[1] and McCuistian et al[7] have studied extensively the use of Griseofulvin for the systemic treatment of dermatomycosis. This antibiotic is derived from certain strains of Penicillium: P. Patulum, P. Griseofulvin and P. Janczewski. Even patients allergic to penicillin usually tolerate the drug without difficulty. However, one of my patients began showing an allergic reaction like that to penicillin after a few weeks of therapy. It is a drug of low toxicity.

Periodic blood counts are recommended for prolonged use, however. The antibiotic was found highly effective in control of infections from Trichophyton, Epidermophyton and Microsporum. Involved sites included the scalp, hands and feet, or nails. The dosage recommended is 200 mgm four times daily for from three weeks to several months. Nail infections require six months of therapy. The drug is deposited in the layers of the skin and must be continued until the involved areas have become excoriated and healthy skin or nail has replaced the diseased. Both Grifulvin and Fulvicin are supplied in 200 mgm tablets.

REPORT OF CASES

CASE 1. M.H.A. This patient, a male, aged 28, is a professional singer. He complained of foggy voice from postnasal drip, nasal obstruction, sneezing and severe itching of the scalp. The latter had been diagnosed by a dermatologist as "more than just dandruff—a fungus infection." On October 25, 1959, Rinkel titrations showed end points on Endo Dust, mold mix (Alternaria, Hormodendrum and Cephalosporium) and T.O.E. Test feeding for corn gave a false positive; because as later observed the Karo corn syrup used had "black mold" growing on it. Later feeding test with new Karo was negative.

The hyposensitization therapy was not successful even with T.O.E. diet control until the T.O. and E. were titrated separately. The scalp condition did not clear until Griseofulvin was prescribed in dosage of 200 mgm four times daily for five weeks. After discontinuing this drug, the scalp lesions again flared with dietary indescretion. Shots have been continued since allergy symptoms develop when they are discontinued.

CASE 2. M.G.D. This male patient, aged 39, has had nasal allergy symptoms for an indefinite number of years and has had "athlete's foot" since childhood. Other symptoms included recurrent dizzy spells, diagnosed as Ménière's disease, cricks in the neck and insomnia with nocturnal nausea. Neurological consultation confirmed the otolaryngologist's diagnosis of Ménière's disease.

Rinkel titrations in February 1959 gave clear end points for Endo Dust, several molds and T.O.E. Response to therapy including dietary control was not good until the T.O. and E. were titrated separately and Griseofulvin 200 mgm four times daily was given. The latter drug was continued for six weeks. The lesions on the feet cleared up, but on discontinuing the drug still flare when the patient goes off his diet. The shots are still required to control his other symptoms.

CASE 3. K.B. This ten-year-old female had a history of chronic sinusitis and skin rash about the legs and buttocks. Four years ago her dermatologist advised tonsillectomy and adenoidectomy to cure the rash. This was performed and the sinusitis was treated but the rash persisted. During the course of the next four years the patient was treated by three more dermatologists, three pediatricians and three different allergists. The rash persisted and the allergists concluded the rash was "not allergic in origin."

On October 24, 1959, the patient was seen in my office again and Rinkel titrations were performed for the first time. She gave clear end points for Endo Dust, T.O.E. and mold mix (Alternaria, Hormodendrum and Cephalosporium). Her ethmoiditis was due to hemolytic staphylococcus aureus and was treated with culture specific Gantrisin. At the same time she was started on Fulvicin (Griseofulvin) 200 mgm four times daily for nine weeks. In addition, Mycostatin 500,000 units four times daily was given for one week. Because of a history of her rash getting worse with the advent of a cold front and weather change, histamine in micro dosage was included with the allergy shots.

At the end of three months utilizing the combined antigenic and antibiotic therapy, her rash had completely cleared for the first time in six years. The ethmoiditis had likewise subsided on Proetz displacement therapy. Five days after discontinuing the antibiotics the rash reappeared.

CASE 4. Mrs. R.A.G. This female patient, aged 40, has had oral and vaginal monilia symptoms for eight years. In addition, she was subject to gastro-intestinal symptoms including difficulty swallowing when certain T.O.E. foods were ingested. Her dermatologist, gynecologist and internist had been unable to cure her trouble. The internist diagnosed hypometabolic euthyroid allergic syndrome and had tried both thyroid extract and tri-iodothyronine without much help. In November 1959 Rinkel titrations showed end points for Hormodendrum, Alternaria, Aspergillus and T.O.E. and therapy was started with injections accordingly. In addition, Nystatin (Mycostatin 500,000 units) was started four times daily by mouth and vaginal suppositories. Also employed was the eight week Godlowski[3,4] regime for hypometabolic state using Prednisolone, multi-vitamins, high protein diet, and tri-iodothyronine (Cytomel) and a tranquillizer.

The patient showed improvement in all her symptoms and again became able to swallow solid foods with a resulting weight gain.

However, after eight weeks of the Mycostatin neither the oral nor vaginal monilia had completely disappeared.

CASE 5. B.W. This male patinet, aged 43 years, has a four-year history of allergy related to T.O.E. and represents the most severe sensitivity I have seen. Multiple symptoms in part or all are present with T.O.E. flare-up. These include malaise, fatigue, nasal obstruction, headache, myositis with "cricks" in back or neck, prostatitis, pruritis ani, genito-urinary manifestations of monilia, nausea, vomiting and "athlete's foot." In addition, overnight gain in weight of as much as five pounds has been noted from acute fluid retention. The skin manifestations have been chronic but the others were present primarily with the ingestion of T.O.E. foods.

Rinkel titrations repeated in September 1959 showed clear end points for Endo Dust, Alternaria, Smuts and T.O.E. Provocative feeding test was strongly positive for T.O.E. foods and negative to other common foods. Results of protein-bound iodine test and sedated basal metabolic rate showed the patient to be hypometabolic. So therapy included Godlowski's regime for euthyroid hypometabolic allergic syndrome (Prednisolone, multi-vitamins, high protein diet, tri-iodothyronine [Cytomel] and tranquillizing drug) for eight weeks. Rinkel's hyposensitization injections of the above antigens were also employed. The T.O.E. antigen had to be administered on separate days from the other antigens, otherwise a flare of symptoms was noted from the combined shot. Also, the T.O. and E. had to be titrated separately to keep from producing symptoms with the T.O.E. injections on any day with or without the other antigens. Different end points were found for each of the T.O. and E. antigens.

Finally the therapy included Griseofulvin 200 mgm four times daily for nine weeks and Mycostatin concurrently for four weeks. It was finally necessary to discontinue the Griseofulvin because the patient began to show allergic symptoms from it, i.e., flaring of the above symptoms as when T.O.E. foods were ingested.

All skin areas cleared with the antibiotics. However, after discontinuing the drug the lesions again flare each time a T.O.E. food is ingested by accident.

CASE 6. Mrs. W.C.W. This female patient, 41 years of age, had a history of recurrent ear, nose and throat symptoms including sinusitis and otitis media. In addition, she was under urological and gynecological care for five years for recurrent genito-urinary infec-

tions and vaginal monilia infections. There were occasional bouts of oral monilia as well.

Studies in March 1959 showed her to be hypometabolic and Rinkel titrations gave end points for mold mix, smuts, Endo Dust, and T.O.E. Provocative feeding tests gave strongly positive reaction to the T.O.E. group, milk, wheat, and Irish potato.

Accordingly, her treatment was started: Godlowski's regime for euthyroid hypometabolic allergic syndrome (Prednisolone, multi-vitamins, high protein diet, tri-iodothyronine (Cytomel) and tranquillizing drug for eight weeks in addition to her dietary control and hyposensitization allergen injections. Griseofulvin 200 mgm four times daily was given for four weeks and Nystatin (Mycostatin) 500,000 units four times daily for eight weeks. No dilution of T.O.E. mixture of individually titrated T.O.E. components could be found which did not flare symptoms. Administration on different days from the other antigens did not solve the problem. So, the T.O.E. injections had to be discontinued. One week later, while continuing the Mycostatin by mouth and vaginal suppositories, monilia had completely cleared. She has remained asymptomatic regarding monilia. However, dietary control and hyposensitization injections, other than T.O.E., are necessary to control the other symptoms. Cystitis or pyelitis, or both, soon result along with nasal and eustachian tube blockage when the offending foods are ingested.

CONCLUSION

It would seem from this small group of six problem T.O.E. allergy cases that the antibiotics, Nystatin for monilia and Griseofulvin for Epidermophyton and Trichophyton, do not represent a valuable adjunct to treatment. No lasting benefit to the allergic syndrome was noted in spite of adequate antibiotic therapy. The development of an "id" reaction must pose specific problems because the dramatic cures reported for regular moniliasis and dermatomycosis cases were not seen. These expensive drugs are not justified in severe T.O.E. allergy cases.

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Appreciation is expressed to the Squibb, McNeill and Schering Pharmaceutical Companies for their cooperation.

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XXVIII

STAPEDOPLASTY

FURTHER OBSERVATIONS

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When Rosen[1] resurrected stapes mobilization surgery, the general prediction was that refixation would inevitably occur. Unfortunately, this proved to be true in a disappointing percentage of cases. However, the results now obtained by more extensive techniques seem to indicate that long range hearing improvement may yet be a possibility.

Fowler[2] conceived the idea that bypassing the lesion was the most desirable approach. When the lesion was limited to the anterior footplate area, he suggested that an anterior crurotomy be performed and that the posterior uninvolved footplate then be separated from the lesion. Good results were obtained by this procedure in selected cases.

Total stapedectomy was revived by Shea.[3] He suggested that, after stapedectomy, the fenestra ovalis be sealed with a vein graft and conduction continuity be re-established with an insert of polyethylene tubing between the incus and the vein graft. Schuknecht[4] uses a fat graft plug to close the fenestra ovalis after stapedectomy and a tantalum wire prosthesis. House[5] has advocated a gelfoam seal together with either a polyethylene or wire prosthesis. All of these techniques require the insertion of a foreign substance into the middle ear. Portman[6] has described using a vein graft under the crura after removal of the footplate.

My efforts and thinking have been inclined toward the use of autogenous tissues to reconstruct an effective conduction channel through the fenestra ovalis. The initial technique consisted of a short anterior crurotomy and a long posterior crurotomy and transposition of the posterior crus to a fragmented central area of the footplate.

Presented at the Meeting of the American College of Surgeons, Southern Section, Louisville, Ky., January 22, 1960.

This has been described as stapedoplasty.[7] Farrior[8] has described a similar technique. Initial results were quite satisfactory, but again a few regressions occurred. However, it was noted that good hearing improvement was retained most frequently when the transposed crus was placed over a footplate in which a dehiscence was created at the time of the fragmentation. Creating an opening in the footplate will be referred to as a stapedotomy if the footplate rim remains intact. The term partial stapedectomy will be used when the entire posterior portion of the footplate is removed.

TECHNIQUE

At the present time, I still carry out a Fowler procedure if the posterior part of the footplate mobilizes during the process of performing an anterior crurotomy. If the posterior part of the footplate is still fixed after the anterior crurotomy is completed, then a partial stapedectomy is planned.

After completing the anterior crurotomy, the posterior crus is separated from the footplate. Every attempt should be made to cut it as long as possible. A fine right angle probe and saw are essential for this step of the technique. Before the partial stapedectomy is completed, a small piece of perichondrium is obtained from the base of the helix, just posterior to the external meatus. This can be done precisely under the microscope. The perichondrium is transferred to the promontory. Partial stapedectomy is completed and the opening closed with the perichondrium plug which should be slightly larger than the opening into the vestibule. The posterior crus, which has been reflected anteriorly or occasionally posteriorly, is then teased back over the perichondrium. The perichondrium here is subcrural in position. In some instances, the posterior crus is annoyingly in the way during this technique. This procedure ideally completed is sketched in Figure 1. The incus attached to the capitulum is not shown. The incudo-stapedial joint must not be torn. Gelfoam (not shown) is placed over the perichondrium graft.

In some instances in which the posterior crus was long and reached the plane of the footplate, no tissue was placed under the transposed crus after partial stapedectomy. The crus "dangled" over the perilymph in the vestibule and the opening was sealed by placing a few small pieces of perichondrium around the crus, i.e., circumcrural. This is shown in the sketch in Figure 2. Gelfoam (not shown) is packed over the perichondrium graft as an added assurance of obtaining a perilymph seal.

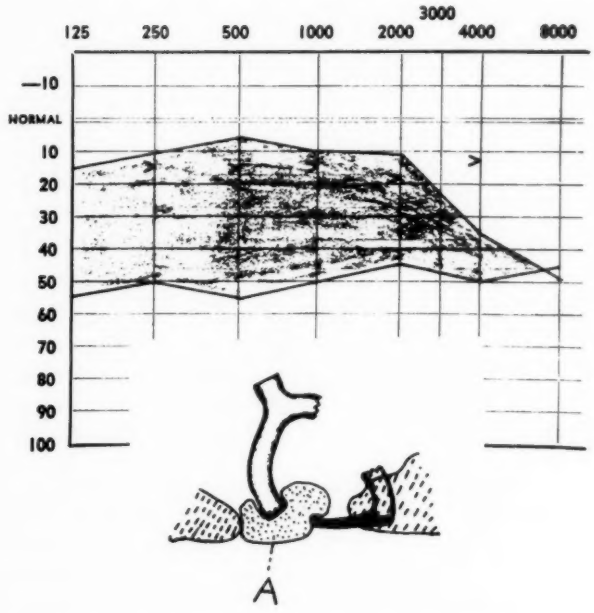

Fig. 1.—A - the perichondrium graft under the posterior crus (subcrural) in the vestibular opening created by the removal of the posterior half of the footplate. Cases 1-4 in Figure 6.

In another group of cases, a small stapedotomy was performed, the opening covered with perichondrium or a small piece of chorda tympani and the posterior crus then placed over the tissue graft. The footplate was usually very thin in these cases. These are represented in Figure 3.

Under miscellaneous techniques are included those cases in which there was either a total footplate mobilization or a posterior crural transposition to a fragmented footplate. When the crus failed to reach the footplate, either a piece of meatal bone or a segment of the chorda tympani nerve was interposed between the crus and the footplate.

RESULTS

This analysis covers a total of 31 consecutive cases on which stapes surgery was performed from July to December, 1959. The selection

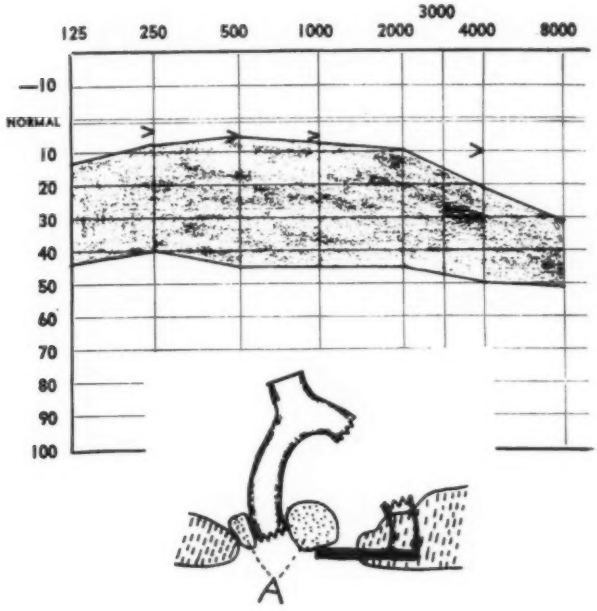

Fig. 2.—The posterior crus "dangles" in the vestibular opening created by the removal of the posterior half of the footplate. The opening is sealed by (A) the circumcrural perichondrium graft. Cases 5-8 in Figure 6.

of technique was varied, depending on anatomy and pathology together with a trend toward partial stapedectomy as the better functional results of this method became apparent. No prosthesis was used in any of the cases inasmuch as I wished to use only autogenous structures.

Each chart shows the average of the preoperative and postoperative air-conduction threshold at each frequency and the preoperative bone conduction threshold for the cases in which each specified technique was used. The preoperative average curve is at the bottom and the postoperative at the top of the shaded area. The shaded area indicates the improvement in hearing as determined by air conduction threshold. The postoperative audiograms used were made from three weeks to two months after surgery, depending on the availability of the patient for follow-up testing. The average preoperative bone conduction threshold is represented by the arrow at each frequency.

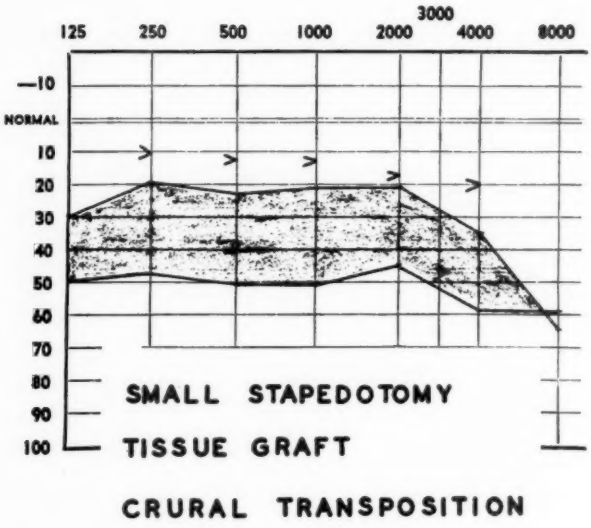

Fig. 3.—Cases 9-15 in Figure 6.

Figure 1 represents the results obtained in four cases in which a subcrural perichondrium plug in the partial stapedectomy opening with crural transposition was used. Complete air-bone gap closure was obtained. These are cases 1-4 in Figure 6.

In Figure 2 are shown the results obtained in four cases in which, after partial stapedectomy, the crus hangs in the vestibular opening and the perichondrium graft is used around (circumcrural) instead of under the crus to seal the vestibule. In this group the air-bone gap is also closed. These cases are number 5-8 in Figure 6.

In seven cases, a small stapedotomy was created and a tissue graft seal and crural transposition placed over the opening. These are shown in Figure 3 and as cases 9-15 in Figure 6. The results are satisfactory but obviously not as good as those in cases 1-8.

Four cases in which the Fowler technique was used are shown in Figure 4 and as cases 16-19 in Figure 6.

The miscellaneous technique group is represented in Figure 5 and as cases 20-31 in Figure 6. Case 22 in this group was a young woman

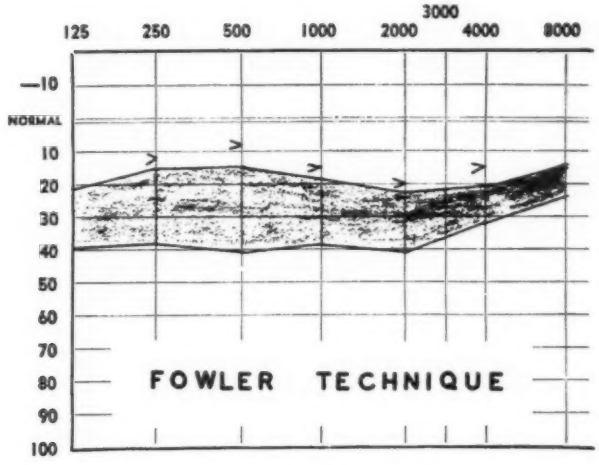

Fig. 4.—Cases 16-19 in Figure 6.

with complete filling of the oval window recess with vascular otosclerotic bone. The bone conduction threshold was normal. I elected not to attempt to remove this extensive lesion at this time inasmuch as I felt that the uncertainty of long range improvement did not warrant the risk to normal cochlear function in this young individual. Should surgery in such cases prove to be of long range benefit, further surgery can be considered at some future time.

COMMENT

It is immediately obvious that the best results were obtained in cases in which partial stapedectomy was performed (Figs. 1 and 2, Cases 1-8 in Fig. 6). In cases in which the postoperative air threshold improved to a better level than the preoperative bone threshold, it was found that the postoperative bone threshold shifted toward zero, and that air and bone thresholds were approximately identical at the improved level of hearing. The bone conduction threshold shift after surgery is not shown in Figures 1-6. Figure 7 shows such a postoperative shift.

Some of the partial stapedectomy cases show considerable high tone loss early after surgery. Figure 7 shows a series of audiograms on such a case. Recovery occurred in a period of about 10 weeks.

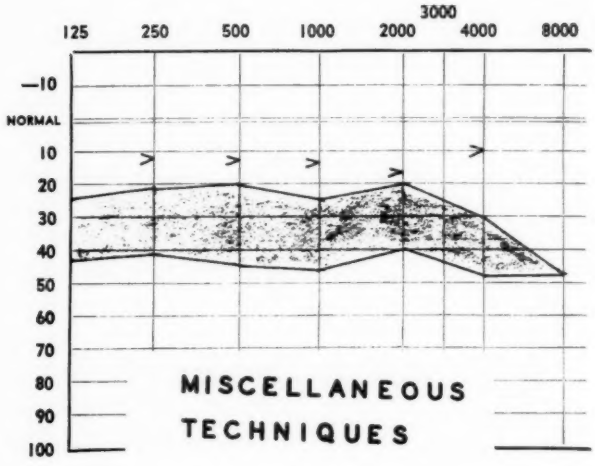

Fig. 5.—Cases 20-31 in Figure 6.

In many cases the 8000 frequency seems to be permanently depressed as indicated in Figures 1, 3 and 5.

In Figure 8 is shown the postoperative audiogram of a partial stapedectomy case in which there was only a minimal high tone depression early after surgery. As a long range study of postoperative labyrinthitis in stapedectomy surgery, it would seem imperative to have early (one week) postoperative audiograms if factors which cause cochlear damage are to be uncovered and avoided in the future.

The tendency for the 8000 frequency not to show improvement after otherwise effective surgery would indicate considerable cochlear morbidity in this area. The cases in Figure 2, however, show a good high tone improvement. Whether this is related to this particular technique or is merely a matter of chance distribution in a small number of cases remains to be determined by further observation. It is encouraging to note that partial stapedectomy is not invariably followed by irreversible high tone depression. The occlusion of the vestibule would seem to be less secure with the technique used in the cases in Figure 2. One might speculate whether a slight perilymph ooze during the first day or two after surgery might create a favorable perilymph decompression or possibly free the vestibule of otherwise detrimental substances. When gelfoam is placed over the perichon-

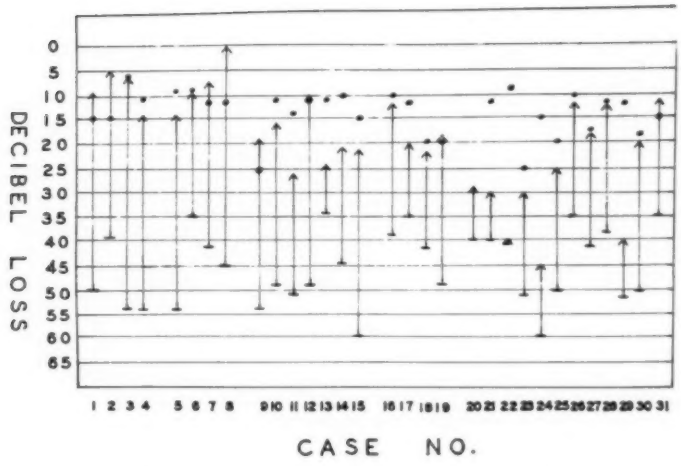

Fig. 6.—Each vertical arrow shows the improvement in hearing as the average of the three speech frequencies (500-1000-2000) of the case number noted at the bottom of the chart. The preoperative bone conduction threshold average for the same frequencies is indicated by the solid dot.

drium graft, it promptly becomes saturated with perilymph by a wick-like effect. It would be interesting to compare early postoperative high tone loss in cases with gelfoam occlusion in contrast to those in which a vein graft was used.

The amount of perilymph which wells up after stapedectomy varies. I plan to study cochlear damage in relation to perilymph welling up to the extent of preventing gravitation of blood, etc. into the vestibule. Should more abundant perilymph be a protection against cochlear damage, jugular vein compression during the stapedectomy might be investigated as a means of increasing perilymph production, providing that bleeding was not increased.

Depression of the higher frequencies on air conduction audiometry after surgery may be due to both middle ear and cochlear factors. Edema of the conduction structures and middle ear effusion will selectively depress the high frequencies more than the low tones on air conduction audiometry due to the mass increase effect. This tends to disappear in a week or two. When present, it probably accounts for not more than 10 or 15 db depression unless the effusion is tenacious and excessive.

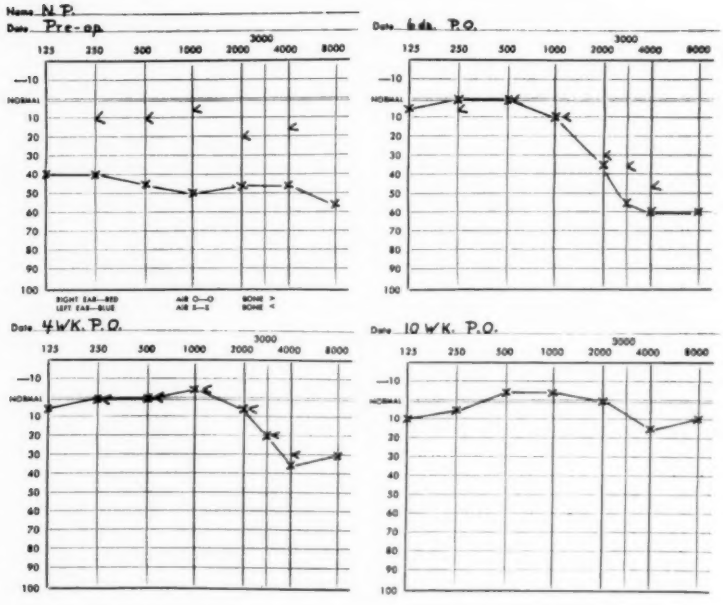

Fig. 7.—Audiograms showing postoperative progress in Case 8.

Severe high tone loss indicates primarily a depression of cochlear function. The following factors must be considered:

1. *Mechanical Trauma at Surgery.* Schuknecht[9] has shown in animals that high tone cochlear damage can result from extensive footplate manipulation. Making a small perforation in the footplate prior to manipulation would obviate this danger somewhat. The need to avoid direct trauma to the saccule and utricle with probes and hooks is obvious and needs no comment.

2. *Biochemical Disturbances during Surgery.* Topical application of local anesthetics to the middle ear structures should be avoided unless the patient experiences pain. Recent experimental studies by Rahm, et al.,[10] indicate that cochlear potential is definitely depressed by topical application of local anesthetics in the middle ear. Certainly, gravitation of meatal anesthesia into the vestibule after stapedectomy is highly undesirable.

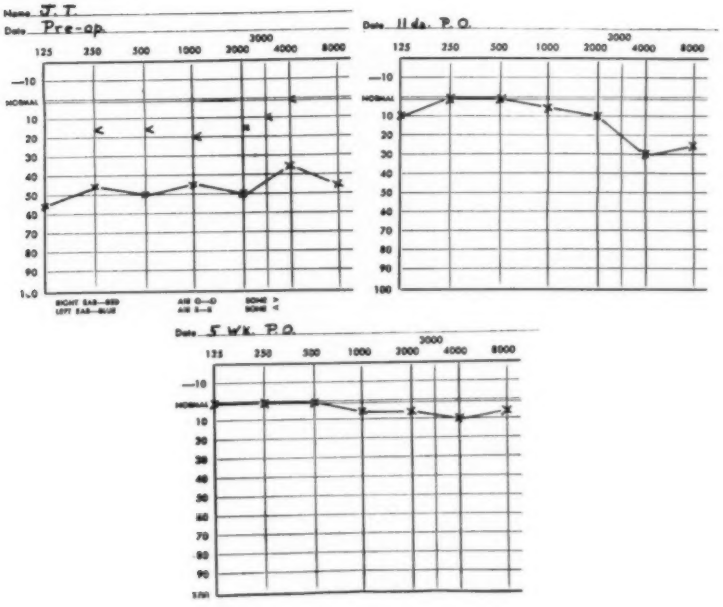

Fig. 8.—Audiograms showing postoperative progress in Case 1.

Mixing any type of irrigating fluid with the perilymph after stapedectomy should be avoided. A minute amount of blood might be less damaging than irrigation.

Gravitation of blood into the vestibule should be avoided by assuring complete hemostasis before stapedectomy. Having the occluding tissue or material available immediately after stapedectomy will decrease the extent of this problem.

3. *Reaction of the Labyrinth and Cochlear Structures to the Tissue Graft or Material Used for Occlusion.* This facet of the problem needs further consideration. A study should be made to compare the reaction to gelfoam in contrast to a tissue graft. A tissue graft should be as fresh as possible. In obtaining the tissue, direct infiltration of anesthetic into the tissue should be avoided in order to decrease the possibility of transfer of the anesthesia solution into the vestibular contents.

Vertigo has been minimal in the cases with partial stapedectomy in this series. The patients have all been able to leave the hospital the day after surgery as far as vertigo is concerned. I keep these patients flat in bed for 24 hours after surgery with the hope of increasing perilymph formation. The possible theoretical reason for this has already been discussed.

Whether partial stapedectomy has any long range advantage over total stapedectomy in decreasing postoperative labyrinthitis can be determined only by extensive comparative studies. It would certainly seem logical that the remaining anterior shelf of the footplate in partial stapedectomy would serve to protect the vestibular contents to some extent. Whether partial or total stapedectomy is best as far as long range maintenance of conduction efficiency is concerned remains to be determined.

The future reaction of otosclerotic bone to the use of a burr or curette remains to be determined. It has been my impression on revisions that all structures appeared to be more hyperemic than they were at the time of the original surgery. Myers, et al.,[11] have noted the same tissue response. If otosclerotic activity reobliterates the oval window in a few years after removing an extensive lesion, then the risk to the cochlear function by burring out the lesion may not be justified.

CONCLUSIONS

1. In the series of cases reviewed, the best results were obtained in those patients in whom a partial stapedectomy was performed, the air-bone gap being completely eliminated.

2. Though the technique is difficult and tedious, an efficient by-pass conduction mechanism (stapedoplasty) can be reconstructed in many patients by using only autogenous tissues.

3. Routine early postoperative audiometric studies should be carried out to point the way to those techniques and other factors which result in the least high tone cochlear morbidity as well as permanent conduction efficiency.

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XXIX

GRANULAR CELL MYOBLASTOMA OF THE LARYNX WITH THE PRESENTATION OF TWO CASES

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Although several theories have been proposed, the exact nature or mode of origin of granular cell myoblastomas has not yet been definitely determined.

Abrikossoff[1] in 1926 was the first person to describe these unusual tumors. However, reports of similar lesions—all arising in the tongue and probably of the same nature—were presented previously in the literature by Weber,[2] Heurtaux,[3] Pendl,[4] Moschcowitz,[5] and Keynes.[6]

HISTOGENESIS

Abrikossoff[1] originally suggested that these tumors arose from adult striated muscle fibers which had undergone degeneration, probably as a result of trauma or inflammation, followed by regeneration with neoplasia of the regenerating muscle cells.

In 1928, Klinge[7] propounded the dysontogenic theory which is based on the similarity of the tumor cell and a granular cell which appears during the normal maturation of the primitive muscle cell. This theory sets forth the belief that these tumors originate from embryonic muscle fibers (primitive myoblasts); in accepting this hypothesis of the myogenous origin of granular cell myoblastomas, one must suppose that those lesions, occurring in areas where striated muscle is not normally found, must develop from embryonic rests of aberrant myoblastic tissue. Klemperer,[8] Crane and Tremblay,[9] and Murray[10] have supported this muscular theory of origin.

Abrikossoff[11] finally adopted Klinge's theory of origin for those tumors arising in areas where no striated muscle is normally found,

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This report has been reviewed by and published with the approval of the United States Public Health Service. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the United States Public Health Service.

but he retained his original belief in the degeneration-regeneration process for myoblastomas found in skeletal musculature.

Gray and Gruenfeld[12] did not believe that there was any resemblance between the tumor cells and embryonic myoblasts. They considered the lingual lesions to be myogenic, but suggested that the tumors arising in the tongue have a different histogenesis than elsewhere. They adhered to Abrikossoff's original concept and maintained that the characteristic tumor cells developed from adult muscle fibers undergoing necrobiotic changes which probably resulted following some mild trauma to the muscle fibers.

In 1939, Leroux and Delarue[13] expressed the opinion that granular cell myoblastomas arose from histiocytes. This concept was supported by Holle,[14] Ringertz,[15] Lauche,[16] and Azzopardi.[17] Azzopardi regards these granular cells as modified tissue cells (histiocytes) which are ingesting and storing some metabolite formed outside of the cells. He believes this abnormal metabolite may be altered myelin in view of his observance of the prominence of nerve elements in many specimens examined by him. Holle[14] believed that this stored metabolite was mucus, while Ringertz[15] and Lauche[16] considered it to be the resultant product of protein breakdown.

In 1948, Fust and Custer[18,19] proposed the theory that these tumors are unusual variants of neurofibromata. This concept of neural origin has been supported by the investigations of Ashburn and Rodger[20] and Bangle.[21,22]

These differing theories indicate that the exact histogenesis is not clearly defined, and the so-called granular cell myoblastoma remains to be the cause of perennial controversy.

There is some divergence of opinion as to the existence of malignant forms of this condition. Malignant granular cell myoblastomas have been reported by Ravich, Stout, and Ravich,[23] Powell,[24] Dunnington,[25] Ceelen[26] and Ross, Miller, and Foote.[27] Azzopardi,[17] however, seriously doubts the neoplastic nature of these lesions. He suggests that many of the tumors reported as malignant myoblastomas in the literature could have really been examples of frank sarcomas, in some cases, rhabdomyosarcomas, in others, spindle-cell sarcomas.

PATHOLOGIC ASPECTS

Myoblastomas, as they occur in the larynx, are usually small, firm, nodular, sessile, and circumscribed. However, some reported

lesions have been lobulated, pedunculated, and polypoid in character. The color may range from gray-white to pink or slightly yellow or tan. These lesions could be mistaken for fibromas.

These tumors grow slowly, and adequate local excision usually suffices with no recurrence of the lesion in most cases. However, Kernan and Cracovaner[28] reported a case in which there was local recurrence of the growth on the vocal cord two months after the initial surgical intervention. The patient was followed closely for two years after the second operation with no further recurrence. MacNaughtan and Fraser[29] also reported recurrence of a granular cell myoblastoma after an initial laryngofissure was done to remove the tumor. A total laryngectomy was finally required in this case in order to obtain a cure.

All reported cases of granular cell myoblastoma of the larynx have been benign histologically. Microscopically, these lesions are composed mainly of medium to large-sized polyhedral cells, the majority of which are irregularly rounded. The distinctive feature of the cell is the presence of abundant pale staining acidophilic granular cytoplasm. The nuclei are usually small, round to oval, vesicular, and centrally located; pyknotic forms may be numerous, but mitoses are usually absent.

Proliferation of the overlying epithelium is a common finding in myoblastomas occurring beneath an epithelial surface. This pseudoepitheliomatous hyperplasia should not be misinterpreted and a diagnosis of squamous cell carcinoma be unjustly made. Horn and Stout[30] reported a case in which the false diagnosis of squamous cell epithelioma of the tongue was made by biopsy, and radium therapy was given before the correct diagnosis of granular cell myoblastoma was established by excision of the lesion at a different hospital than where the original biopsy was done. Hyperplasia of the overlying epithelium was recorded in at least 13 of the reported 21 cases of laryngeal granular cell myoblastoma. (The two cases presented in this paper are included.)

CLINICAL ASPECTS

Myoblastomas are uncommon tumors; the tongue is most commonly involved, with the skin and subcutaneous tissue, alveolar processes, respiratory tract, breast, ear, and lip being affected in a decreasing order of frequency.

Of approximately 300 csases of reported granular cell myoblastoma appearing in the literature, 19 of these have been found occur-

ring in the larynx, mainly on the vocal cords. The two cases presented in this paper constitute the twentieth and twenty-first reported cases of laryngeal granular cell myoblastoma.

The principal symptom recorded is hoarseness, and this may be present from 1 to 2 years before the lesion is detected. Dyspnea, stridor, and hemoptysis have been reported occasionally. In Maguda and Young's[31] case, no local laryngeal symptoms were present, and the lesion was discovered during a routine investigation of frontal headaches.

Although these tumors have occurred in all age groups, the greatest incidence of cases occurs in the third, fourth, and fifth decades.

There is no definite sex predilection for the general occurrence of these lesions, but the incidence in reported laryngeal cases shows a ratio of 14:5, with more males being affected than females. (The sex determination in two cases was not reported.)

TREATMENT

The usual treatment of these lesions consists of local surgical excision with removal of an adequate margin of tissue by means of the direct laryngoscopy technique and use of the biting forceps. In four cases, laryngofissure was done initially to remove the tumor.[29,32-34] In MacNaughtan and Fraser's[29] case, a total laryngectomy was finally done because of local tumor recurrence after an initial laryngofissure had been performed, and irradiation therapy had failed to destroy the lesion. As mentioned previously, there have been only two reported cases of recurrence of the laryngeal lesion after initial surgery.[28,29]

These tumors have low radiosensitivity. Irradiation therapy was used in a case in which the granular cell myoblastoma arose in the tongue,[30] and in another case in which the lesion originated on the posterior wall of the larynx;[29] in both cases, there was no significant change.

REPORT OF CASES

CASE 1. B.P., a 60 year old white male merchant seaman, was admitted to the United States Public Health Service Hospital, Staten Island, New York, on April 23, 1956, with the chief complaint of hoarseness and dyspnea of eight weeks' duration. Six weeks prior to his hospital admission, the patient had had a laryngeal biopsy performed in Italy, and was told that an operation should be done because

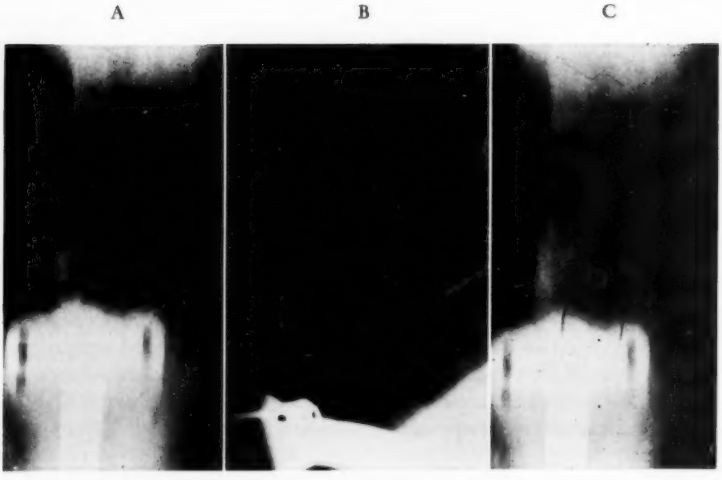

Fig. 1.—(A) This photograph shows one of the x-rays taken during tomography of the larynx. A large irregularly rounded air shadow (laryngocele) is seen lying above the level of the vocal cords. Notice the soft tissue mass (granular cell myoblastoma) which is indenting this air containing shadow. (B) A lateral view of the neck showing the laryngocele. (C) This is the same photograph as *A* except that the intratracheal and intralaryngeal spaces as well as the locations of the laryngocele and granular cell myoblastoma have been outlined. (1) intratracheal space, (2) right vocal cord, (3) intralaryngeal space, (4) granular cell myoblastoma, (5) laryngocele.

of a possible malignant lesion of the larynx. The patient had decided to return to the United States for treatment.

Physical exam revealed a well-developed, well-nourished, white male in a moderate amount of respiratory distress. Indirect mirror laryngoscopy revealed a large cyst-like bulging in the general area of the left laryngeal ventricle. The remainder of the physical exam was not remarkable.

On April 27, 1956, a routine orderly tracheostomy was done to relieve the patient's dyspnea.

On May 10, 1956, a direct laryngoscopy, under topical cocaine anesthesia, was done; a large, easily-indented, cystic lesion, protruding from the left ventricular area, was seen. It was not possible to grasp the wall of the lesion with the laryngeal forceps, so the cyst was

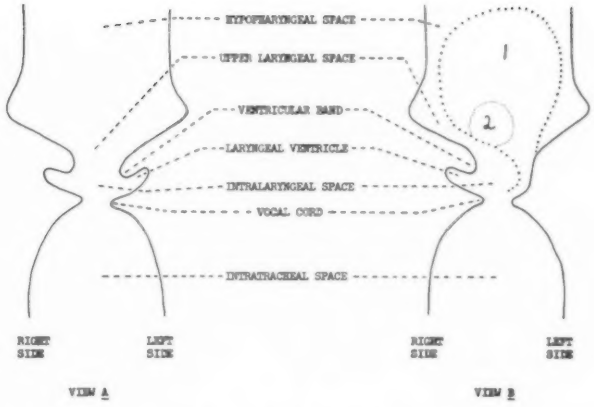

Fig. 2.—Enlarged outlined drawings of the larynx in coronal section showing the hypopharyngeal, intralaryngeal, and intratracheal spaces. View A shows the normal outline of these spaces. View B is a coronal section through the laryngocele and its communication with the left laryngeal ventricle. The laryngocele is indicated by No. 1 of View B. The granular cell myoblastoma which is attached near the neck of the laryngocele is indicated by No. 2 of View B. The left laryngeal ventricle has been deformed by the laryngocele.

pierced with a small needle, but it was not possible to aspirate any material through the needle.

On May 22, 1956, laryngeal tomograms were done revealing a large, irregularly rounded laryngocele (4x4 cm) which communicated with the left laryngeal ventricle (Fig. 1).

On May 23, 1956, a left lateral laryngotomy was performed under a general endotracheal anesthesia. The soft tissues over the left portions of the hyoid bone and larynx were dissected free, and the left lateral aspect of the hyoid bone and the superior lateral portion of the left lamina of the thyroid cartilage were removed, revealing the bulging laryngocele. The external surface of the laryngocele was dissected free from the surrounding tissues, and the sac was traced down to a very narrow neck which communicated with the left laryngeal ventricle. There was a small, soft, tan node (1.5x1.5x1 cm) attached near the neck of the laryngocele (Fig. 2). The neck of the laryngocele was ligated with fine chromic catgut, and the redundant sac and adjoining node were excised. The wound incision was closed in layers; the entire procedure was tolerated well by the patient.

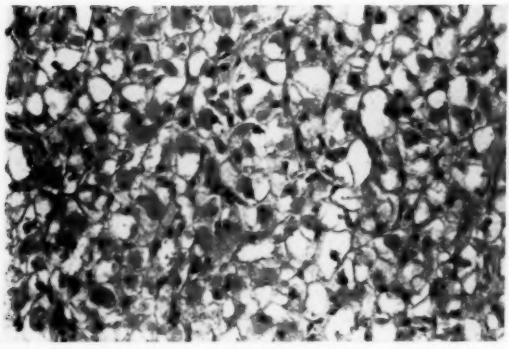

Fig. 3.—Photomicrograph showing a lattice-work pattern with the spaces occupied by cells with round irregularly placed nuclei and granular cytoplasm. (H. & E. x 150).

The removed specimen was submitted to the pathology department for diagnosis. One portion of the specimen was diagnosed as being consistent with the wall of a laryngocele. However, microscopic examination of the small node, removed with the laryngocele sac, revealed a lattice-work pattern with the spaces occupied by granular pinkish-staining cells which had irregularly placed nuclei. This portion of the submitted specimen was diagnosed as a granular cell myoblastoma. (Sections of this specimen were submitted to the Armed Forces Institute of Pathology staff for confirmatory diagnosis; they concluded that it belonged to the group of granular cell myoblastomas in spite of the considerable vacuolization of the cells.) (Fig. 3).

Postoperatively, the patient's voice improved considerably, and he was discharged from the hospital on June 27, 1956, at which time the tracheostomy opening had closed completely, and the wound incision had healed satisfactorily.

I have examined this patient at periodic intervals since his discharge from the hospital, and to date, there has been no evidence of any recurrence of the granular cell myoblastoma or laryngocele.

CASE 2. J.R., a 31 year old white male, was admitted to the United States Public Health Service Hospital, Staten Island, New York, on March 5, 1958, with the chief complaint of hoarseness of

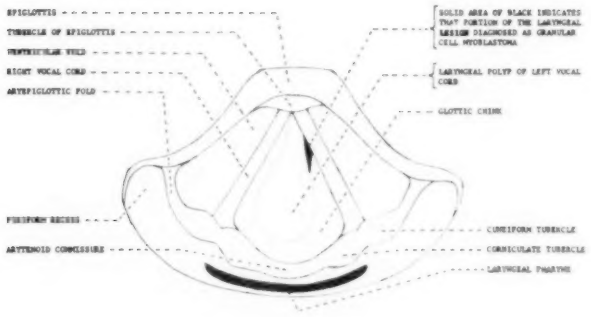

Fig. 4.—Enlarged outlined drawing of the indirect mirror view of the interior of the larynx. The location of the vocal cord lesion (area enclosed by black dotted line) is shown. That portion of the laryngeal lesion diagnosed as granular cell myoblastoma is indicated.

approximately 15 years' duration. The patient indicated that he had always had a weak voice as a child, and about 1943, he developed a husky voice with intermittent bouts of hoarseness which would last approximately two weeks and then disappear. In 1949, he entered the Army as a sergeant, and the hoarseness became more marked due to excessive use of his voice. For eight months prior to his hospital admission, constant hoarseness (worse in the morning) was present with occasional bouts of aphonia, requiring several forceful coughs to restore the voice to a hoarse caliper. He developed a sensation of "something in this throat" which he thought he could cough up. There was no history of hemoptysis, dyspnea, or pain.

Approximately one week prior to his hospital admission, the patient was admitted to another hospital where the diagnosis of a laryngeal polyp was made; the patient was then referred to our hospital for further evaluation and treatment.

The patient's family history revealed that his father had died of carcinoma of the larynx at the age of 58, and his mother had had a laryngectomy because of a laryngeal carcinoma. One sister, age 34, was living and well.

The physical examination revealed a well-developed, well-nourished, white male with a very weak and hoarse voice. His neck was quite short and muscular. Indirect mirror examination revealed a

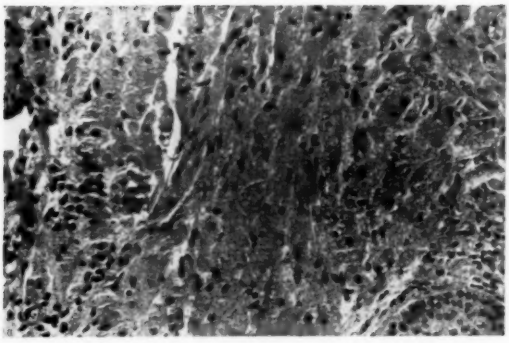

Fig. 5.—Photomicrograph showing abundant closely packed large cells with somewhat granular cytoplasm. Epithelial hyperplasia of a small duct is shown in the right lower corner of the photograph. (H. & E. x 150).

large pedunculated, pinkish-gray lesion arising from the anterior third of the left vocal cord. The growth appeared to be about 2.5x1x.5 cm in size (Fig. 4). Both vocal cords were thickened. The remainder of the physical examination was not remarkable.

On March 10, 1958, under 5% topical cocaine anesthesia, a direct laryngoscopy was done, and approximately 75 per cent of the laryngeal lesion was removed by using biting forceps. A small tag of the growth was left attached to the anterior third of the left vocal cord, as the patient developed some laryngospasm making further attempts to remove the remainder of the lesion impossible.

The removed specimen was submitted to the pathology department for diagnosis. The gross lesion was polypoid in shape and covered by a glistening gray membrane. Microscopically, there were two components of the lesion. One portion appeared to be a usual laryngeal polyp. There was some proliferation of the overlying epithelium, and in a few areas, this showed slight to moderate atypia, but none of this alteration approached malignant degree.

The other smaller component of the lesion showed closely packed large cells in the stroma. These cells had abundant acidophilic and somewhat granular cytoplasm. The nuclei were round to oval and showed slight to moderate variation in size. This component of the lesion was diagnosed as a granular cell myoblastoma (Fig. 5).

The pathologist commented that these lesions were often associated with pseudoepitheliomatous hyperplasia of the overlying epidermis and the atypical epithelial proliferation in this case might be related.

On March 13, 1958, a repeat direct laryngoscopy under 5% topical cocaine anesthesia was done, and with the patient in the Kernan position, the remaining portion of the lesion was removed completely by using biting forceps. The base attachment of the lesion to the anterior third of the left vocal cord was cauterized with 10% silver nitrate.

Microscopic examination of the tissue removed during the second procedure proved it to be the remaining portion of the laryngeal polyp, and no component of the granular cell myoblastoma was seen.

The patient's postoperative course was uneventful, and there was a marked improvement in his voice, although it was still somewhat weak in character. The patient was discharged from the hospital on March 24, 1958, at which time an indirect mirror laryngoscopy revealed no evidence of any laryngeal lesion. The cords were thickened bilaterally, but the anterior commissure and anterior third of the left vocal cord were perfectly clean. The patient was instructed on how to practice certain voice exercises in order to attempt to strengthen his voice.

At the time of writing this report, there has been no evidence of any recurrence.

SUMMARY

Granular cell myoblastomas, while still uncommon, should not be classified with the rarest tumors.

The exact histogenesis of these tumors has not yet been definitely determined, but several theories (myogenic, histiocytic, and neurogenic) have been proposed to explain their origin.

Myoblastomas, as they occur in the larynx, are usually small, firm, and nodular. The principal recorded symptom produced by these tumors has been hoarseness. Adequate local excision usually suffices with no recurrence of the lesion; radiation therapy has no effect.

All reported laryngeal granular cell myoblastomas have been benign histologically. A significant finding in the microscopic exam-

ination of these tumors has been a proliferation of the epithelium overlying these growths.

Nineteen cases of granular cell myoblastoma of the larynx have been reported in the literature. The twentieth and twenty-first reported cases are presented in this paper.

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I wish to extend my appreciation to Drs. James Gould, John Glotfelty, Theodore Perrin, Mr. Kenneth Donohue, and Miss Vera Mitchell for their helpful assistance.

Addendum. This paper was presented at the annual meeting of the United States Public Health Service Clinical Society at New Orleans, Louisiana, on April 3, 1959.

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XXX

AN UNUSUAL CASE OF ADENOCYSTIC CARCINOMA OF THE PAROTID GLAND

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Adenocystic carcinoma, also commonly known as cylindroma and cystic basiloid carcinoma, comprises about ten per cent of all malignant parotid tumors. Most patients are middle aged. The most common symptoms are local swelling, pain, and facial paralysis. The average duration of symptoms is five years. Growth is slow, but eventually the tumor infiltrates muscle, cartilage and bone. Metastases, usually late, sometimes appear in the lung and remain there without causing symptoms for years. Other sites of metastases are the regional lymph nodes and less frequently, osseous structures.

REPORT OF A CASE

Mrs. E.C., a 38 year old housewife, entered University Hospital in November 1959, complaining of diminished hearing in the right ear and intermittent pain deep in the ear. She also complained that the right side of her face was weak.

Her first symptoms had come four months before and were related to the ear. She had a fullness in the right ear and decreased hearing. Shortly thereafter there was an intermittent dull ache in the ear. She was treated by her otolaryngologist who performed a myringotomy and found serum in the middle ear. An audiogram showed a 20 decibel conductive type hearing loss in the right ear. The patient failed to return for additional investigation at that time. Four months later, in November, she was seen again with the same complaints and in addition there was a palsy of the right facial nerve.

From the Department of Otolaryngology, The Ohio State University, Columbus, Ohio.

Fig. 1.—Incomplete facial paralysis.

Fig. 2.—Tenderness in retromandibular area. Note that there is no tumor visible in parotid area.

She was admitted to her local hospital. A roentgenogram of chest showed multiple large bilateral pulmonary lesions, probably metastatic. Routine laboratory tests were normal. First strength PPD and histoplasmin skin tests were negative. At this time the patient was referred to the service of Dr. William H. Saunders at the Ohio State University Medical Center.

Physical Examination. The patient seemed undernourished although she denied any weight loss in the past two years. Vital signs were normal. Positive physical findings were limited to the head and neck. There was an incomplete peripheral facial paralysis on the right (Fig. 1). All other cranial nerves were intact.

The parotid gland was not enlarged but there was moderate tenderness in the right retromandibular area (Fig. 2).

There was severe retraction of the right tympanic membrane and serous fluid in the middle ear. On the anterior wall of the external auditory canal just adjacent to the tympanic membrane there was a small mass (4x6 mm). It was grey, non-tender, and did not bleed on gentle probing. The left ear was normal. The Weber test lateralized to the right, the Rinne test was negative on the right.

Laboratory Studies. Routine laboratory studies including the serologic test for syphilis, blood count and urinalysis were normal.

Roentgenograms. The chest film showed metastatic lesions throughout both lung fields (Fig. 3).

A parotid sialogram was normal.

Stereoroentgenograms of the base of the skull showed an extensive destructive process of the greater wing of the right sphenoid. The destruction included the anterior wall of the external auditory canal, the foramen ovale, the foramen spinosum and the foramen lacerum (Fig. 4). Mastoid films showed haziness of the right mastoid cells. The haziness was felt to be compatible with the patient's serous otitis media which was caused by pressure of the tumor on the eustachian tube.

Course in the Hospital. The patient remained in University Hospital six days. There were no changes in the ear symptoms or the facial palsy. No additional symptoms or signs appeared during hospitalization.

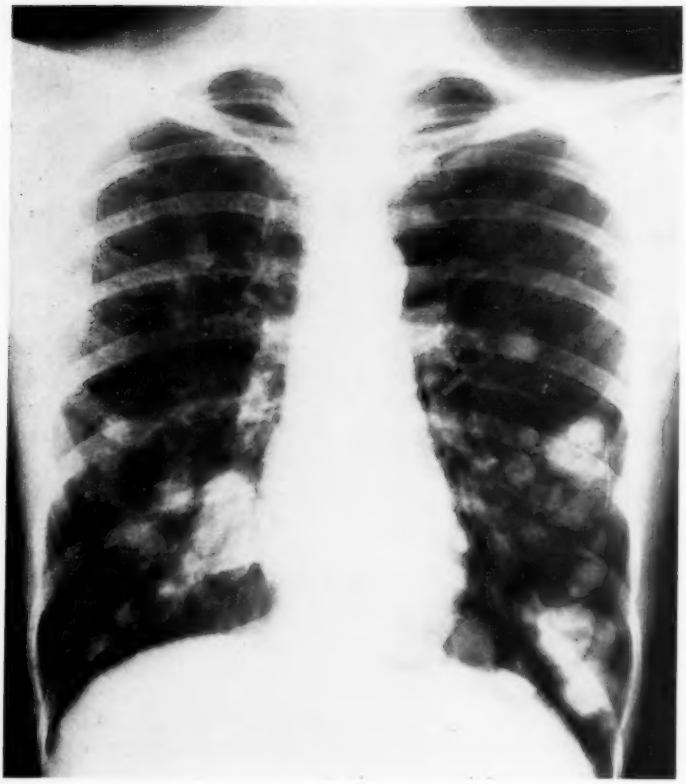

Fig. 3.—Multiple chest metastases are clearly seen.

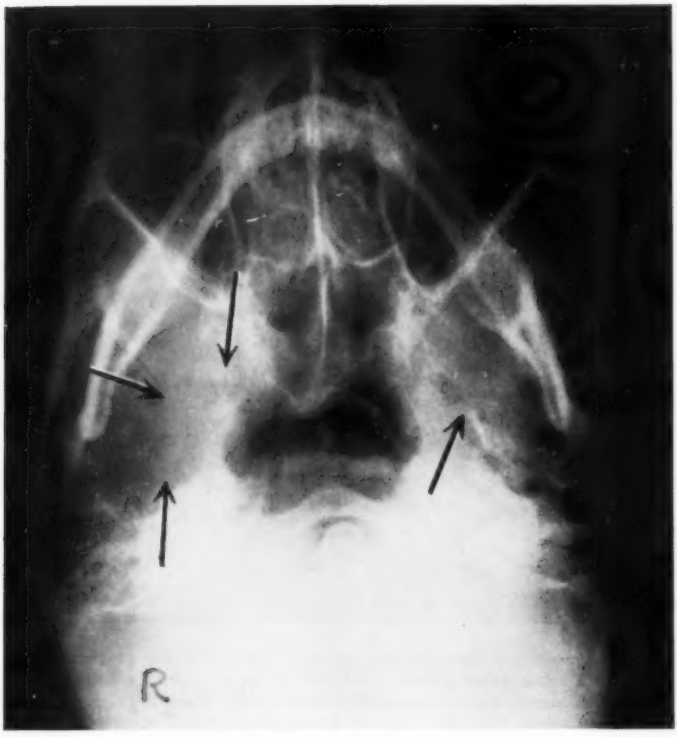

Fig. 4.—Destruction of base of skull. The three grouped arrows indicate the destroyed area. The single arrow on the other side points to normal foramen ovale and foramen spinosum.

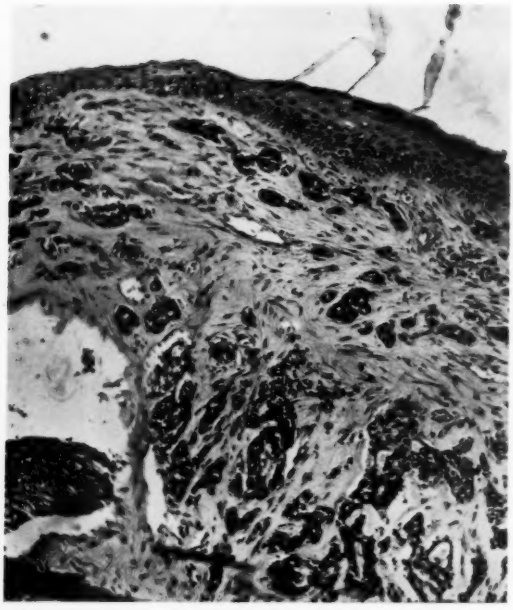

Fig. 5.—Biopsy from external auditory canal. Masses of tumor cells are seen in subepithelial tissues. Cells are all similar and show no pleomorphism. Note occasional cystic spaces in cell masses. These are characteristic. Superficial masses probably represent lymphatic or blood vessel permeation. H & E X 125.

Under local anesthesia the tiny tumor in the inner aspect of the external auditory canal was removed for examination. The pathologist reported adenocystic carcinoma (Fig. 5). This tumor has a myriad of names, some of the more common of which are cylindroma, cystic basiloid carcinoma and pseudoadenomatous basal cell carcinoma.

The patient was discharged to the care of her own otolaryngologist. It was suggested that she begin a course of palliative irradiation therapy to the parotid area.

COMMENT

This case is presented to emphasize several points.

1. Cylindroma of the parotid may metastasize to the lung and remain asymptomatic for many years. This unusual behavior has been pointed out by other authors. How long our patient had had her pulmonary metastases is unknown but she was entirely unaware of any chest disease when we saw her.

2. A tumor of the parotid need not always present as a mass palpable externally or in the pharynx. Sometimes, as in this patient, a tumor may erode into the ear canal or obstruct the eustachian tube but produce no externally demonstrable mass.

3. Massive destruction of the base of the skull is possible without producing neurological impairment. The facial paralysis seen in this patient was thought to be caused by involvement of the facial nerve deep in the parotid gland.

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XXXI

THE ROLE OF TRAUMA IN THE PATHOGENESIS OF TEMPOROMANDIBULAR JOINT ARTHROSIS

EKREM GOZUM, M.D.

MINOT, N. D.

The temporomandibular joint, because of its location, draws the attention in many branches of medicine. Costen's[4-7] work stressed the importance of temporomandibular joint disease in clinical otolaryngology.

Various theories have been advanced to explain arthrosis of this joint. Trauma has been mentioned by several authors as the most important factor.[16,27]

In this paper the relation of trauma to the mandible and its eventual effect on the joint will be evaluated.

ANATOMY

The joint is formed by the articulating surfaces of the temporal bone (fossa articularis) and the condyloid process of the mandible.

The articulating surface of the temporal bone is situated anterior to the tympanic bone; it is separated from the latter by the squamotympanic fissure. This fissure is divided medially into two fissures by the protruding edge of the roof of the tympanic cavity, an anterior petrosquamous fissure and the posterior petrotympanic fissure.

The chorda tympani and the anterior tympanic artery descend through the latter fissure; this anatomical relation is very important in the symptomatology of temporomandibular arthrosis.[5]

The posterior portion of the articular fossa is elevated to a ridge; this eminence limits posterior displacement of the condyle. In cases

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From the Minot Eye, Ear, Nose and Throat Clinic, Minot, N. D.
Read before the College of Surgeons, North Dakota Chapter, 1958.

of fracture of the condyle, the ridge, also, protects the tympanic plate from being fractured by the displaced condyle. The anterior portion of the fossa is formed by the eminentia articularis which according to Lubotsch[19] is more prominent in men than in women. This anatomical finding is thought to be the cause of the higher incidence of temporomandibular joint arthrosis in the female.

The condyle forms the articulating surface of the mandible. It is about 15-20 mm long and 8-10 mm thick. The facet is strongly convex anteroposteriorly and slightly convex mediolaterally.

The temporomandibular joint is divided into two compartments, a considerably larger upper and a smaller lower compartment, the meniscus is a fibrocartilagenous plate which is thicker at the circumference and thinner at the center. It has been reported by some textbooks as being perforated at the center. Wakeley[31] in one hundred dissections never found a single perforated disc. Nargaard in 112 arthrographies of the temporomandibular joint reported 28 perforated discs.[22]

Each compartment is supplied with a synovial capsule. The fibers of the capsule are denser between the disc and the condyle; therefore, extensive sliding motion occurs in the upper compartment.

PHYSIOLOGY

Three different movements are observed in this joint: a) hinge-like motion, b) forward sliding (symmetrical protrusion), c) asymmetrical lateral excursion.

The hinge-like motion of the mandible is a complicated one as the condyle is moved in a vertical plane; a forward sliding of the meniscus occurs simultaneously. Condyles are shifted forward and downward due to bilateral contraction of the external pterygoids. In symmetrical protrusion the mandible moves forward and downward when the front teeth pass the corresponding incisors then proceeds in an upward and forward motion. Gliding motion is formed by the anterior displacement of the condyle and the rotation of the axis of the condyle.

In the asymmetrical lateral excursion, the condyle is pulled toward the articular tubercle as the mandible moves around a vertical axis.

PATHOLOGY

Degenerative joint disease has been thoroughly studied by Bauer[1] who summarizes histological changes as follows: in the first stage the connective tissue lining of the articular surfaces becomes irregular and shows signs of degeneration, edematous foci of calcification may develop in the area of necrosis.

In the second stage, the irregular surfaces develop into cleft formation; detached collagenous fibers are seen in the joint cavity. In the third stage the fibrous tissue disappears and the bone marrow spaces are exposed. Hemorrhages and minute fractures of the bony trabeculae in the joint occur. The fibrocartilaginous disc may be destroyed in this period.

During the final stage, the proliferation of the connective tissue obliterates the cavity. According to Bauer, the marginal exostoses are the most characteristic features of the osteo-arthritis deformans.

PATHOGENESIS OF TEMPOROMANDIDULAR ARTHROSIS

Temporomandibular disease is a disease of middle and old age, there is no hereditary disposition in the etiology of the disease. It is more frequently seen in women. Lubosch's[19] findings are thought to be a factor in this higher incidence. Malocclusion has been considered a very frequent cause of temporomandibular arthrosis.[20,28] Infection has been accepted as the most important cause of the ankylosis of this joint.[23,24,29]

SYMPTOMS OF TEMPOROMANDIBULAR ARTHROSIS

The most prominent symptom in the early stage is pain, the intensity is variable. It may radiate into the surrounding tissues or distally to the mandible and the neck.

A metallic taste or burning sensation in the tongue may be experienced, clicking of the joint is frequently felt; in some cases it is audible. A conductive hearing loss may be present.[28]

DIFFERENTIAL DIAGNOSIS

Arthrosis of the temporomandibular joint is differentiated from arthritis through history and clinical laboratory findings. Sedimentation rate is normal in arthrosis and antistreptolysin titer shows no

change. Roentgen examination is conclusive, tomography is used for the diagnosis of the fibroankylosis of the joint.[12,25] Arthrographic studies are also used for the diagnosis.[22]

TREATMENT

Temporomandibular joint disease is treated medically and surgically. In the acute stage, pain is alleviated with narcotics, oral, or intra-articular cortisone administration usually gives dramatic improvement of the symptoms. 0.5-1 cc cortisone is injected into the superior compartment of the joint, this is repeated every ten days three or four times.

Various surgical methods have been described.[14,16,17,21,23,26,27] In cases of extensive motion of the condyle, sclerosing substance injection has been widely used in the past.

If the condyle movement is extremely restricted removal of the articular disc may be considered.[3,9]

Orthodontic treatment arrests the progress of the disease and it is the treatment of choice. With the proper repositioning of the mandible a conductive hearing improvement as much as 15-20 decibels can be obtained.[28]

MATERIAL

Fifty-eight cases of fracture of the mandible and three cases of acute trauma to the mandible without fracture were obtained from the files of the Ancker Hospital. These cases occurred during the years of 1942-1954. One case included is from 1956 as an example of the early occurrence of the disease.

Patients were recalled (only 45 of the patients could be located), careful interim histories were obtained, physical examination was done. In suspected cases roentgen examinations of the temporomandibular joint in mouth open and closed positions were carried on.

The youngest patient was 7 years old and the oldest 57.

Four cases developed demonstrable temporomandibular joint arthrosis. Five patients complained of pain around the joint, crepitation was experienced in three cases and earache in four.

TABLE I

DISTRIBUTION OF THE CASES ACCORDING TO YEARS

1942	-	4
1943	-	6
1944	-	4
1945	-	6
1946	-	7
1947	-	5
1948	-	2
1949	-	6
1950	-	2
1951	-	1
1952	-	4
1953	-	6
1954	-	4

TABLE II

DISTRIBUTION OF THE CASES ACCORDING TO DECADES

0-10	-	1
10-20	-	4
20-30	-	18
30-40	-	16
40-50	-	10
50-60	-	9

TABLE III

CLASSIFICATION OF THE CASES BY SITE OF FRACTURE

LOCATION	NO.	UNILATERAL	BILATERAL	DISPLACEMENT
Symphysis	3	3		1 case 0.5 cm
Body	18	13	5	3 cases 0.5 cm
Ascending ramus	10	4	6	2 cases 0.5-1 cm
Angle	8	4	4	4 *
Condyle	7	3	4	2 cases ant.
Condyle-Body	4			
Angle-Ramus	5			
Condyle-Symphysis	2			
Angle-Symphysis	1			

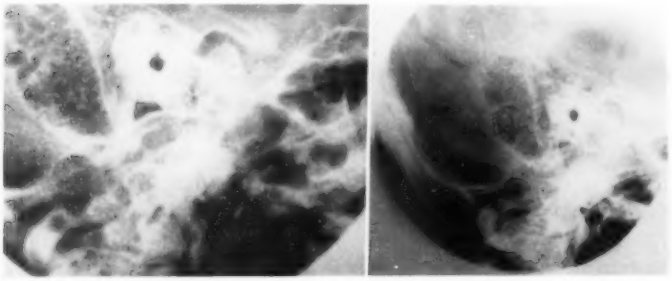
REPORT OF CASES

CASE 1. Mrs. K.S., No. 140610. The patient was involved in a car accident in 1946. Multiple lacerations of the face were repaired on an emergency basis. On physical examination, a large hematoma was noticed on the left side of the mandible, considerable pain and trismus were observed. Skull x-rays were negative; roentgen exam-

ination of the facial bones revealed comminuted fracture of the left angle of the mandible with slight displacement of the proximal end. Similar findings were seen on the right side without separation and displacement.

The fracture was treated by intermaxillary wiring, the wires were kept on for five weeks. The patient was seen on February 10, 1956. Her history revealed pain over the left temporomandibular joint area and crepitation on the involved side.

Examination revealed limited condylar movement on the left side, deviation of the chin to the left when mouth opened. X-ray examination revealed a normal right temporomandibular joint (Fig. 1, A). The left joint was found narrowed and cloudy (Fig. 1, B).



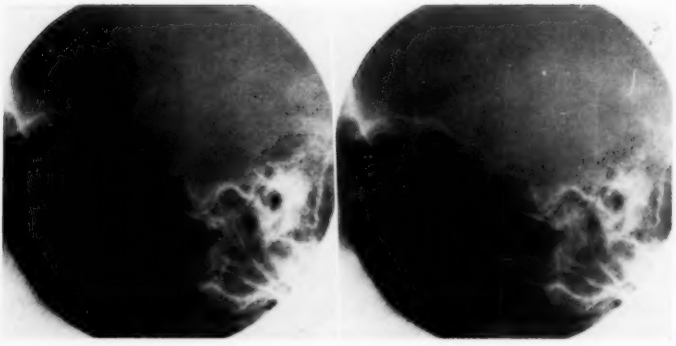
A B

Figure 1

CASE 2. Mr. H.E., No. 135287. The patient was seen in the receiving room on July 29, 1953, with a history of trauma to the left side of the jaw. He complained of severe pain and marked trismus.

Physical examination revealed a large hematoma on the left side of the mandible, the oral cavity revealed laceration of the mucosa due to the fracture of the mandible. X-ray examination revealed a comminuted fracture of the left ramus of the mandible.

The patient was treated with intermaxillary wiring. He did not show up until December 24, 1953, for follow up. He was seen in



A B

Figure 2

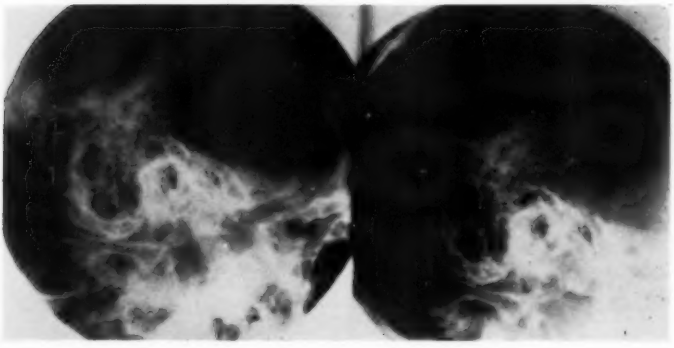
the receiving room with a history of a direct trauma to the jaw one week previous.

Physical examination showed a large fluctuating mass on the left side of the mandible. The patient had a temperature of 101°F. X-ray examination revealed a sequestration of the body of the mandible with abscess formation. The abscess ruptured spontaneously the following morning, the patient was treated with antibiotics, no surgery was done because pulmonary disease was present.

The patient was seen again on March 10, 1955, with the main complaint of pain over the right temporomandibular joint. Examination revealed a bony defect measuring 4 cm in length on the left side of the mandibular arch. The patient was treated with bone grafting and intermaxillary wiring. On January 19, 1956, roentgen examination showed absorption of the bone graft. He again had pain over the right temporomandibular joint.

X-ray examination of the temporomandibular joint revealed flattening of the condyle and the joint space was found enlarged (Fig. 2-A). Diminished motion of the right condyle is seen in Figure 2-B.

CASE 3. Mr. C.W.L. No. 113120. The patient is an old epileptic. In 1947, during a seizure he fell, fracturing his jaw. He was seen in the emergency room, multiple facial lacerations were sutured.



A - Mouth closed B - Mouth open

Figure 3

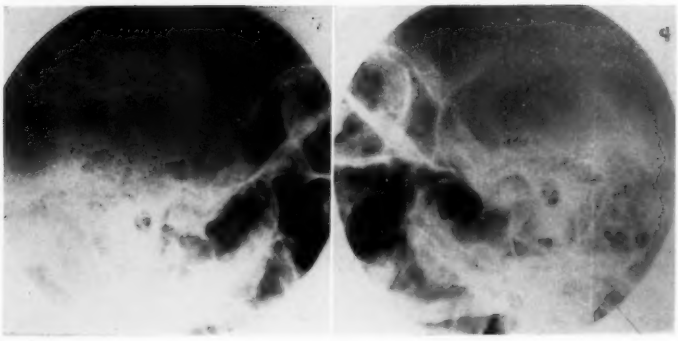
Physical examination revealed hematoma over the right side of the mandible. X-ray studies showed a comminuted fracture of the ascending ramus of the mandible.

He was treated with intermaxillary wiring. When he was seen on January 5, 1956, he complained of pain in the right temporomandibular joint and earache on the same side. Examination revealed retarded motion of the condyle, deviation of the chin to the right when mouth opened.

Roentgen studies revealed extreme narrowing of the joint space.

Figure 3-A shows increased calcification. Figure 3-B shows flattening of the condyle.

CASE 4. Mr. H.S. No. 193781. This 36 year old Mexican laborer was seen in the out-patient department on April 20, 1956, with the main complaint of severe pain over the right temporomandibular joint. Questioning revealed that the patient had a severe acute trauma over the jaw a year earlier. Physical examination demonstrated a deviation of the chin to the right when mouth opened and diminished motion of the right condyle. Laboratory examination revealed normal findings. X-ray studies of the joint revealed a marked narrowing of the right temporomandibular joint space, Figure 4-A. The left joint, Figure 4-B, is normal.



A B

Figure 4

COMMENT

Review of the literature revealed no work done regarding the incidence of temporomandibular joint arthrosis in healthy people selected at random. Foged[9] on examination of 2400 hospital patients, found snapping in 2% of the cases. Lotsch[18] examined a special group of men (230 policemen) and found snapping existed in 5% of the cases. Boman's[3] work shows no different incidence in the occurrence of temporomandibular joint arthrosis in people with good or bad molar support. He again found no higher incidence of temporomandibular joint arthrosis in different bites.

European and American medical and dental literature of the past thirty years reveals no statistical studies of the importance of acute trauma in relation to the development of temporomandibular joint arthrosis. During the same period several cases of temporomandibular joint arthrosis were ascribed to acute trauma but no statistics were compiled. I believe acute trauma is an important cause of temporomandibular joint arthrosis. Trauma of different intensity produces variable changes in the joint and articular disc. Damage to the fibers of the articulating surfaces and disc, fracture of the disc or microscopic fractures of the subcondyle bony surfaces occur or damage to the capillaries and hemarthrosis of the joint may occur as a result of acute trauma. Destruction of the articular lining surface and exudation of the fibrin into the articular cavity diminishes the elas-

ticity of the joint surfaces restricting the gliding motion of the joint; later arthrosis may develop.

According to Goodfriend[10,11] and Hiltebrandt[13] the articular disc is the most important structure in the absorption of the trauma. Certainly excessive trauma may traumatize the disc and thus further damage results in the long run.

If the trauma is severe enough to cause fracture of the mandible, the masticatory muscles further complicate the clinical picture. They exert their influence on the respective fragments, thus the elevator group will pull the proximal end of the fracture anterior superiorly and medially, suprahyoids will pull the distal fragment anteriorly and downward. In cases of comminuted fractures of the condyle, the latter is apt to be displaced anteriorly by the contraction of the external pterygoid muscles. With the anterior superior displacement of the proximal fragment the condyle is pressed on the articular disc and the tympanic plate. This is true for the fractures above the level of the angle.

If the ideal repositioning is not obtained in these cases, the condyle, as a result of anterior displacement, may cause continuous trauma on the disc and fossa articularis.

Analysis of the cases revealed the incidence of arthrosis was much higher in cases of comminuted fractures of the ascending ramus and the condyle with displacement.

In fracture of the ascending ramus if the fracture line extends from inferior-anterior to superior-posterior, the proximal fragment of the fractured mandible will be pulled antero-medially and superiorly. It is obvious that fractures of the ascending ramus of the mandible require special attention in re-positioning. In comminuted fractures distal to the angle of the mandible, the distal end is pulled downward and anteriorly by the suprahyoid group. In the presence of the teeth good occlusion is easily obtained with intermaxillary wiring. The cuspids and canines are not as essential for the position of the condyle in the temporomandibular fossa, thus the chance of malocclusion is diminished in these cases.

In case of fracture (crushing of the disc), the removal of the disc is justified.

Finally, the number of patients developing symptoms of temporomandibular arthrosis shows the importance of acute trauma and the

effect of continuous trauma and in some cases malocclusion on the joint in causing the disease. Considering this, the importance of open reduction in cases of comminuted fractures of the mandible with displacement is seen.

SUMMARY

Fifty-eight cases of fracture of the mandible and three cases of trauma without fractured mandible are reviewed, the incidence of temporomandibular joint arthrosis is analyzed.

It is found that temporomandibular joint arthrosis was seen more often in cases of fracture of the ascending ramus and the condyle.

The importance of acute trauma in the production of temporomandibular joint arthrosis is stressed.

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XXXII

BLOOD LOSS DURING ADENOIDECTOMY AND TONSILLECTOMY MEASURED WITH RADIOISOTOPES

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Blood loss during adenoidectomy and tonsillectomy has been studied in several ways in the past[1] but has not been followed with the radioisotopes, insofar as the author of this paper has been able to discover. Blood volume and blood loss have been investigated for other surgical procedures in the past few years, since the radioisotopes have become available for qualified laboratories. The purpose of this paper is to study the blood loss during the tonsil surgery as measured by radioactive chromium and radio-iodinated serum albumin, in a group of 17 patients.

With ordinary clinical precautions of recognizing potential bleeders and the use of modern surgical techniques in a well organized and well equipped hospital, there is little likelihood of severe hemorrhage. This report is intended to record the technique and results of an interesting study, which is of limited practical value to the practicing otolaryngologist.

A summary of the bibliographic material available and the technique of measuring blood volume with radioisotopes will be given. Briefly stated, the principle involved is comparing the number of disintegrations per minute in a given volume of the standard to those of a similar volume of the patient's blood which has been injected with the radioisotope. The ratio of the two counts equals the ratio of the standard solution in its diluted form to the unknown blood volume; this equation may then be solved for the blood volume.

Isotopes[2] (from the Greek *isos* and *topos*, meaning the same place, i.e., the same place in the periodic table) are atoms of a given element which differ in the number of neutrons in the nucleus. Some isotopes

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This thesis was presented as a candidate's thesis to the American Laryngological, Rhinological and Otological Society, October 1, 1958. From the Claude Foster Research Laboratories, Department of Surgery, St. Luke's Hospital, Cleveland, Ohio.

are radioactive and may emit more than one type of radiation. For example, I^{131} or radioactive iodine isotope emits beta radiation 87.2% of the time, then with a complex system of decay, emits other types of beta and gamma radiation. Radioactive chromium (Cr^{51}) or rachromate has a more complex system of decay.

The curie is a unit of radioactivity defined in terms of the number of atoms of a given substance which disintegrate in one second; one curie equals 3.7×10^{10} disintegrations. A millicurie is 3.7×10^{7} and a microcurie is 3.7×10^{4} disintegrations per second. The time for 50% of a radioisotope to decay is called the half life, and for radioactive iodine is 8.14 days, and for radioactive chromium is 26 days. The relationship between the radiation intensity in milliroentgens per hour at a given distance and the number of millicuries of activity for I^{131} is 0.225.

Radiation is counted in the laboratory using a scintillation counter which consists of a scintillator crystal; the crystal emits flashes of light when exposed to radiation, and these flashes are counted by a photomultiplier tube which amplifies these flashes to a point where measurable bursts of electrons are produced and recorded by an electronic scaler and count rate meter.

CHROMIUM

The clinical application of Cr^{51} has gained in popularity since 1952 with respect to its tagging of the red cell. Wennesland[3] found a standard deviation of paired determinations in a series of 25 cases checked two or three times to be within 100 cc of red cells, with biological factors being of more importance than technical errors. Rappaport[4] found that the tagged cell method agreed well with other methods in the measurement of cardiac output. Mollison[5] used simultaneous experiments with Cr^{51} and P^{32} labeled red cells and found good agreement, and that the tracer doses used resulted in one-tenth of the maximum daily dose of radiation regularly allowed. Kurtz[6] emphasized that only the intravascular space is measured due to stable binding and that a single injection of Cr^{51} permits repeated blood volume studies over a 24 hour period. Ebough[7] advised the use of whole blood for survival studies rather than saline washed cells which had a 30% less survival time. Eadie[7] used red cells from the same donor for three different recipients and checked the survival by Cr^{51} and the Ashby technique, and found a greater drop in the first 24 hours, greater than would be accounted for by elution, senescence or random destruction. No toxic effects of Cr^{51} were noted. Abajian[9]

used the Cr^{51} method to obtain better blood volume control of the patients especially in major cancer surgery.

Cooper[10] measured bleeding into the intestinal tract by studying the Cr^{51} in the blood and feces. Gibson[11] pointed out that tagging can aid one in determining the viability of stored red cells when used as a posttransfusion study. Meyer[12] suggested the tagging of a supply of O Rh negative cells at the beginning of a week and used these for all red cell volume determinations; repeated tests on the same patients showed a variation of less than 7%.

Technique. Rachromate[13] is available as a neutral, sterile and assayed solution, with 500 microcurie per cubic centimeter at the time of preparation and with a half-life of 26 days. The activity at the time of injection is secured from the decay chart. Into a suitable sterile rubber-stoppered bottle the ACD solution, enough Rachromate to contain 10 microcuries of activity per cc, and 50 cc of the patient's blood is drawn. The bottle is gently agitated for ten minutes to allow tagging of the red cells. A fresh 50 cc syringe is weighed dry and then used to withdraw 30 cc of the Rachromate tagged blood, which is injected into the patient. The syringe is again weighed to give the exact weight of the blood injected. From the tagged blood left in the bottle, one may determine the specific gravity and the hematocrit, and dilute one cc of this to 500, to be used as the standard for comparison with the patient's blood. After ten minutes following the injection of the blood into the patient have elapsed to allow mixing, five cc of the patient's blood is withdrawn, and exactly one cc pipetted into a test tube which is placed into the counter. The ratio between the counts per minute per cc of the standard and the sample equals the ratio between the volume of the standard and the volume of the sample; this equation may be solved for the volume of the patient's blood. From this five cc portion are measured the hematocrit and radioactivity of the whole red blood and plasma, and thus the counts injected into a given volume of red cells are calculated:

$$\text{Total blood counts per min. (T)} = \text{Cts/cc blood} \times \text{Volume}$$

$$\text{Total plasma counts per min. injected (P)} = (\text{Cts/cc plasma injected}) \times \text{Volume} \times \frac{100 - \text{Hct.}}{100}$$

$$\text{Total red cell counts injected (C)} = (\text{T}) - (\text{P})$$

The hematocrit of this sample differs from the patient's blood because of the addition of reagents. With care in centrifuging and

washing it should be possible to count the activity per cc of red cells directly rather than using the above indirect method. If the circulation time is normal, equilibration is completed after 15 minutes and samples may be taken thereafter at any time. The syringe is heparinized to prevent clotting. Two samples are taken at 20 minute intervals and the hematocrit measured. Four to 8 cc samples are centrifuged and the plasma carefully removed; the cells are counted in a well type scintillation detector. If desired, the whole blood and plasma can also be counted as a check:

$$\text{Cts/min/cc packed cells (R)} = \frac{\text{Cts in sample of whole blood}}{\text{Volume of sample}} \times \frac{100}{\text{Hct.}}$$

The red cell volume expressed as cubic centimeters is C/R using the values above. If the cells are counted directly, no hematocrit correction is necessary for R.

One may also separate the red cells before tagging and then centrifuge and wash them thoroughly after tagging. Cr^{51} utilization is better and the calculations are simpler, but the chance of contamination is greater and the pyrogenic reactions more apt to occur.

Patients with gastrointestinal bleeding can have their red cells tagged with as much as 200 microcuries of Rachromate and the blood loss in the stool determined by direct counting of appropriate aliquots of homogenized stool samples. Meyer[14] pointed out that the hematocrit determination from a peripheral vein is a notoriously poor index of the amount of red cells.

Thistlethwaite[15] noted that circulating blood volume is a dynamic quantity which can be measured reliably by Cr^{51}, and tends to remain fairly constant for 24 hours, although it may increase as much as 500 cc following meals or ingestion of large quantities of fluids, but returns to the original value in three or four hours. The volume is somewhat higher at night because of the relative hypotension and decreased renal filtration. During anesthesia the blood pressure may drop, with a rise in blood volume. When hypertension was induced with neosynephrin, the blood volume decreased and the hematocrit increased. Chromium tagged red cells and Risa* measure two different spaces in the body: the former measures the central circulating blood volume, with a higher hematocrit than the peripheral or capillary blood vol-

* Risa,® radio-iodinated human serum albumin (Abbott Laboratories).

ume. With hypotension and vasodilatation there is further dilution of the Cr tagged cells, for they spread to the peripheral blood volume.

Risa measures a space 10 to 40 per cent larger than the Cr tagged cells. Changes in arteriolar tone have little effect on the Risa volumes. Risa leaks into the albumin pool and parts of it are no longer available to the circulation, accounting for the increases in Risa measured volume if taken over a period of hours. For this reason we used two injections of Risa in our studies on the blood loss during adenoidectomy and tonsillectomy. In the data obtained during and after surgery when Risa was used, there was a tendency for progressive increases in the Risa blood volume. These increases occurred more rapidly than those seen in serial determinations in unoperated patients. The operative trauma was thought to produce leakage in the albumin pool. The changes in blood pressure and Rachromate blood volumes were not reliably correlated with the Risa method.

Stanton[16] mentioned that the depleted plasma volume is compensated rather promptly and completely, whereas a depleted red cell volume is restored by the body in a limited manner. In the adequately hydrated patient the hematocrit on the third postoperative day is a useful index of uncompensated red cell loss.

Gurney and Bolt[17] noted that the simultaneous use of Rachromate and Risa in blood volume determinations showed, in summation, the result to be smaller than with the use of Risa alone, and greater than that calculated from the red cell and hematocrit alone. The ratio of total body hematocrit to peripheral hematocrit varied between 0.62 and 0.92.

Read and Gilbertsen[18] noted that there is a constant relationship between true body hematocrit and observed cell plasma ratio. There is some disparity between the large and small vessel hematocrit values, due to the lack of uniformity of distribution of cells and plasma throughout the blood stream. The results of their study indicate that the total body hematocrit derived from the red cell volume and plasma volume data tends to be lower than that found in previous work with standard plasma volume tracers.

Rains[1] mentions several methods of measuring blood by other means: the weighing of sponges and adding the blood in the suction bottle have practical value. Washing the sponges is not practically accurate. Weighing the patient before and after is of some value, but one must add a loss of an additional 30 cc/hour of body fluid through the skin and another 20 cc/hour through the lung. Blood volume

estimations with Evans blue and measured with a Hilger absorptiometer makes consistent results difficult to obtain. In adding a unit of blood it must be remembered that there is about 360 cc of actual blood in the bottle plus 180 cc of citrate solution.

Baker[19] felt that surface area is the most useful single basis for determining the estimated total plasma volume when Risa is used, i.e., 2.68 liters per square meter.

Wicklander[20] discussed the inadequacy of calculation of blood volume from standard values per kilogram of body weight, due to the influence of variations in body fat content. The total blood volume is independent of hemoglobin; the plasma volume and hemoglobin are inversely correlated in normal hydration. Dehydration is suspected when the plasma volume per kilogram is below the standard value.

Karlberry and Lind[21] described a method of obtaining the total amount of hemoglobin in children to eliminate the errors of fingertip determination in abnormality of blood volume. Using a known small quantity of carbon monoxide introduced into a rebreathing system, the amounts of carboxyhemoglobin before and after the addition of carbon can be measured accurately. The amount of carboxyhemoglobin is well below the toxic limits. The blood volume may be calculated by dividing the total carboxyhemoglobin times 100, by the carboxyhemoglobin in grams per 100 cc. There is a close relationship between body weight and blood volume up to 20 kilograms; thereafter the blood volume increases more rapidly than the weight but retains the rectilinear relationship.

RISA

Risa is a trade name[22] for a sterile and pyrogen-free solution of radio-iodinated (I^{131}) human serum albumin, known as IHSA. Not more than one atom of iodine per 60,000 molecular weights of albumin is introduced by mild iodination, so that the physical and chemical properties are unchanged. There is no significant electrophoretic pattern change following the procedure, and there is no exchange of activity to other blood proteins. Risa contains from 0.3 to 0.7 millicurie/cc and about 10 mg of albumin per cc. Because of the slow liberation of iodide the preparation is refrigerated and should be used within four weeks of the date of preparation. By comparing the ratio of the volume of the diluted Risa standard to the volume of the patient's blood with the ratio of the counts per minute of the standard to the counts per minute of the patient's blood, the volume of the patient's blood may be found.

Lugol's solution may be used to block the uptake of iodine by the thyroid gland, although in our series the amount was insignificant. It has been shown that plasma volumes determined by the Risa technique and by the dye T-1824 are practically identical, but the latter is of little value in long term determinations because it is lost too rapidly from the plasma.

After injection of one cc of diluted Risa, ten minutes is allowed for mixing. The blood sample is withdrawn from the patient and the number of counts per minute per cc determined by a well type scintillation counter which permits the use of as little as 3-5 microcuries per patient. The plasma volume may be determined by centrifuging the sample before dilution and the supernatant plasma counted after thorough mixing. Where repeated determinations are carried out on the same patient, one must measure the base line residual activity before injecting a new dose of tagged albumin. This residual activity is then subtracted from the activity of subsequent samples before making the final calculation.

Metabolic studies in animals and humans have shown that detectable amounts of Risa remain in the blood stream and lymphatic system for as long as six days. Complete mixing in the circulating blood occurs within ten minutes. Activity is detected in the thoracic duct within a few minutes. The blood and lymphatic systems reach equilibrium within 7 to 13 hours, but no activity is found in the spinal fluid. Ninety-one and five-tenths per cent of the activity remains in the plasma for one hour after injection; in five hours there is 80%; in 24 hours 45% remains. At the end of 72 hours there is still 32% remaining.

The urine is the main route of elimination of I^{131}, and at the end of the first day after injection the excretion may reach from 5 to 15% of the total amount given. About 5% of the dose administered is taken up by the thyroid during the first 24 hours. It is recommended that the dose or summation of doses per day not exceed 25 to 30 microcuries. Risa is shipped with a stated assay at a given time which falls off according to a decay table.

Beierwaltes, Johnson and Solari[2] state that during the exposure of serum albumin to nascent radioiodine under proper conditions the I^{131} will combine with tyrosine molecules of the albumin to form moniodotyrozine and thus label the serum albumin without altering chemical or immunologic properties of the protein as tested by various means. Repeated plasma volume determinations with Risa in the same

normal individual gave a standard deviation of 173 cc. Blood volume may be estimated from a nomogram relating blood volume to body surface area or to height. It is important to flush the syringe used to inject the Risa with blood to insure getting all the radioactivity into the blood stream.

Spencer, Thistlethwaite, and Alber[23] reported a continuous and simplified blood volume determination by injecting Risa or Rachromate initially, and then running blood from another vein through a polyethylene tube which passes through a scintillation counter and through a syringe for aspiration. The system is equipped with flushing valves and normal saline to keep residual activity from being deposited in the tubing. The system seems to be relatively independent of temperature and barometric pressure changes. This method indicated that complete mixing occurred after 15 minutes following injection. Fifteen to twenty microcuries of the isotope were used initially, and the total for serial determinations should not exceed 250 microcuries.

Our present study consisted of six preliminary attempts with the Rachromate method of studying blood loss during adenoidectomy and tonsillectomy. As soon as the first plane of anesthesia had been reached a 5 cc sample of blood was withdrawn, followed by the injection of one cc of Rachromate tagged cells, using the same venipuncture needle. After ten minutes had elapsed to allow mixing in the body a second sample was withdrawn into a heparinized tube and gently rotated. At the conclusion of the operation a third sample was drawn. The amount of blood lost was measured by measuring that in the suction bottle minus the known amount of rinse water. The amount of blood in the sponges was also estimated by weighing the blood soaked sponges and deducting the weight of an equal number of dry sponges. The first sample was saved for study of the hematocrit.

The second sample was placed in a scintillation counter in the amount of one cc, and the number of counts per minute measured to determine the initial blood volume. The third sample was measured in a similar method to find the final blood volume; the difference between these two figures represented the amount of blood lost. The formula used in these calculations was:

$$\text{Blood Volume} = \frac{\text{Counts of standard} \times \text{cc administered} \times 500 - \text{background}}{\text{Counts of specimen} - \text{background}}$$

Figure 1

The 500 factor is the dilution factor which is used because the standard Rachromate tagged blood registers a much higher count than the specimen, leading to inaccuracies. By diluting the standard, the two values are more nearly approximated and thus more accurately counted. With these six cases the disparity between the radioisotope measurement and the gross measurement was so great that it was decided not to continue this phase any further. Apparently for blood losses in the vicinity of 100 cc the method is not sufficiently accurate.

We turned next to the Risa or radio-iodinated serum albumin method and found that the disparity between the Risa and the gross method was much less, hence we developed our series of cases with the Risa technique.

Briefly then, our method consisted of waiting until the patient reached the first plane of anesthesia, and was well stabilized, and then injecting one cc of the previously prepared and standardized Risa. After waiting ten minues to allow for proper mixing the number one sample for the baseline determination was withdrawn into a heparinized tube using the equipment shown in Figure 1.

The adenoidectomy and tonsillectomy were performed using the Davis mouth gag. The Trendelenburg position was used to prevent

Figure 2

Figure 3

loss of blood by aspiration and swallowing. The anterior pillar was incised 2 mm from its medial border, inferiorly and superiorly to curve around to the posterior pillar. The Hurd dissector was used to dissect the tonsil down to the base of the tongue while exerting medial tension with the tenaculum. The tonsil was snared off and a dry 2x2 inch sponge folded into the fossa. The opposite tonsil was removed in a similar manner. The adenoid mass was palpated and examined directly with the palate retractor, and then removed with the Barnhill curette. The adenoid fossa was again examined by palpation and direct vision with care taken to observe the removal around the torus tubarius. Two 2x2 inch sponges were packed into the fossa. The first tonsillar fossa was observed after removing the sponge. If any bleeding was still present, it was stopped with a sponge wrung dry of adrenalin and dipped into tannic acid powder. The other fossae were treated similarly. If active bleeding persisted, sutures of 3-0 chromic catgut were used to control it. With this method we rarely had to resort to sutures; the incidence of postoperative bleeding was no higher than with other methods, and the duration of the procedure was shortened considerably. By encouraging the patients to increase greatly their intake of sugar and vitamin C for two days preoperatively, the incidence of postoperative emeses is reduced considerably by increasing the storage of glycogen in the liver.

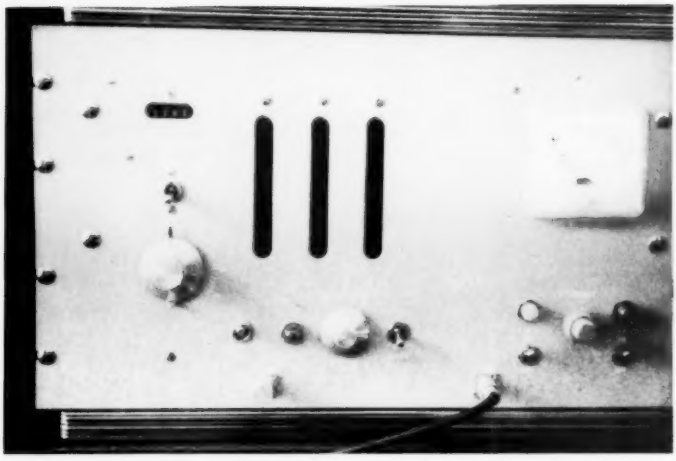

Figure 4

At the conclusion of this procedure another one cc sample of blood is withdrawn and using the same needle a second one cc of Risa is injected. After the ten minute mixing period has elapsed, the third sample of blood is withdrawn and labeled. All of these venipunctures are done during anesthesia, which is most helpful with children.

The three samples are then taken to the laboratory for counting and the values used in the following formula:

$$\text{Blood Volume} = \frac{\text{Counts per min. of standard} \times \text{cc administered} \times 500 - \text{background}}{\text{Counts per min. of specimen} - \text{background}}$$

The background count is obtained by placing an empty tube in the well type scintillation counter seen in Figure 2, and running the counter, Figure 3, for one minute. The count may be read from the scaler, Figure 4, in the window in the upper left corner for the count in thousands, and in the three vertical windows for the hundred, ten and single values.

Correction is made for the second one cc of Risa, which must be injected to obtain greater accuracy since the value of Risa counts

TABLE I

PATIENT	AGE	WEIGHT IN LBS.	HEIGHT IN CM.	EST. BL. VOLUME	OPER. TIME MIN.	GROSS LOSS	RISA LOSS	% DIFF.	% BL. VOL. LOST
J.G.	6	40	110	1100	40	153	167	8.4	15.0
J.G.	7	60	127	1700	28	95	121	21.5	7.1
J.G.	8	60	135	2000	33	84	57	32.0	4.2
G.J.	6	42	109	1090	65	80	93	14.0	8.5
C.B.	8	48	133	1900	32	82	77	11.0	4.0
V.C.	5	39	101	1000	55	61	54	11.5	5.4
S.O.	6	39	107	1050	27	108	118	6.8	10.1
D.H.	12	90	147	2600	70	223	243	8.2	9.3
S.C.	9	67	127	1750	75	120	134	10.5	7.7
B.C.	9	53	125	1600	80	118			7.4
B.T.	6	47	114	1300	25	97	146	31.0	11.2
P.K.	12	83	152	2600	20	111	140	22.0	5.4
J.L.	12	77	147	2400	25	116	112	3.0	4.7
D.G.	6	46	112	1300	25	107	99	7.5	8.2
E.L.	15	109	166	3300	30	86	93	2.6	8.2
J.M.	3	40	101	1000	21	93	83	12.0	9.3
T.H.	7	53	121	1500	54	280	305	8.2	20.0
AVERAGE								11.2%	12.1%

drops so rapidly over a period of hours. There is no danger of radiation effects with Risa because of its short half life and the low 7-10 microcurie radiation, especially when one considers that the dial of a luminous wristwatch forms a radiation of 30 microcurie constantly. From a nomogram (Brines, Gibson, and Kunkel[24]) one may calculate the ideal blood volume using the upper lines, and the plasma volume from the lower lines, knowing the height in centimeters.

COMMENT

The accompanying table is a listing of patients including their vital statistics and the results of the blood loss during the adenoidectomy and tonsillectomy as measured by collecting the blood in a suction bottle, deducting the water used for rinsing the suction, and adding the blood absorbed by the sponges that were blood soaked,

deducting the weight of an equivalent number of dry sponges and multiplying the result by 1.055, the specific gravity of blood. These figures were added and entered in the "gross loss" column. The losses measured by the Risa method as described earlier in the paper were entered under the "Risa loss" column. The differences between the Risa and gross losses were entered under "error" and expressed also as percent error. Finally the estimated blood volume was calculated so that the percentage of blood lost during the procedure could be calculated and entered as percent of the total blood volume lost. One may speculate as to the value of keeping data on all adenoidectomy and tonsillectomy procedures and suggest to those patients who have lost more than the usual amount of blood, that hematinic medication be started immediately to aid in recovery.

It is of interest that the accuracy of the two methods is open to some question; where the Risa method gave a higher reading, it was noted by the surgeon that there was considerable blood swallowed and possibly aspirated during the procedure, thus escaping measurement by the gross method, although with the Trendelenburg position this factor was minimal. A considerable amount of blood may be aspirated unknowingly as pointed out by radio-opaque oil studies by May, Thoburn and Rosenberger.[25] It is rather difficult to explain the excess of the gross method over the Risa; here a small error may produce a considerably larger error in the final counting procedure. There is some error possible in the method of counting the samples by the scintillometer; the leaking of the albumin in and out of the albumin pool could certainly affect the final count, especially if the procedure was time consuming. The largest errors were not necessarily seen with the longest operations.

One of the most frequent problems encountered was the small size of the young patient's veins, which made four venipunctures very trying. This problem would be greater were it not for the fact that the venipunctures are all done during anesthesia.

If the surgeon has sufficient trained personnel in the operating room, the procedure goes smoothly, but when the surgeon attempts to perform the injections and then do the surgery, difficulties arise.

SUMMARY AND CONCLUSIONS

1. Three ways of measuring blood loss during adenoidectomy and tonsillectomy are presented in this paper, the first two not having been reported previously:

A) Radioactive chromium is used to measure blood volume and blood loss during surgery.

B) Radioactive iodinated serum albumin is used to measure blood volume and the loss during surgery.

C) Gross measurement of the blood in the sponges and suction bottle is correlated with the above two.

2. The chromium method is of too little accuracy to be used with the small amounts of blood lost in this procedure.

3. The accuracy of the Risa method as compared with the gross method varied from a difference of 3% to 32% in a series of 17 procedures, with an average of 13%.

4. The amount of blood lost varied from 61 cc or 11.5% and 77 cc or 4% of the total blood volume to 305 cc or 20% of the total volume. The average loss was 12.1% of the total blood volume.

5. The Risa method has practical value in following the course of a surgical problem in which blood loss is a factor, and may be used in unusual cases where a greater amount of blood may be expected to be lost. However, for the usual adenoidectomy and tonsillectomy it becomes rather cumbersome unless enough trained personnel are available, and the veins of the patients are large and sturdy enough to withstand a minimum of four venipunctures. One may follow the daily blood volume with the Risa method, where continual loss of blood volume is suspected, with greater accuracy than with the hematocrit of hemoglobin methods in common use, as pointed out by other authors. With larger amounts of Risa injected the accuracy of the method increases, as does the hazard of radiation.

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XXXIII

THE STRUCTURE OF NERVE ELEMENTS IN THE MAJOR SALIVARY GLANDS OF THE HUMAN

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The nature and distribution of nerve endings in the major salivary glands has been extensively studied histologically by many investigators. The greater portion of this work consisted of animal studies which included the owl, porcupine, rabbit, cat, dog and cattle. Investigation of human salivary gland parenchyma was the exception rather than the rule. While all evidence herein is demonstrated by photomicrographs, all known previous publications presented drawings in support of findings.

These studies are exclusively from human parotid and submaxillary salivary gland tissue obtained at the operating table from patients requiring surgical removal for either benign mixed tumors or sialolithiasis. Sections chosen for this study were grossly and histologically normal salivary gland parenchyma. Twelve specimens were selected; six parotid and six submaxillary glands. The illustrations are from two specimens of parotid glands and of two submaxillary glands.

METHODS OF STUDY

All specimens were fixed in 10 per cent neutral formalin immediately after surgical removal and sectioned one to three weeks later on a freezing microtome at 15 microns. Sections of all specimens were stained with hematoxylin and eosin for normal histologic definition. The silver impregnation techniques utilized were those of Gros-

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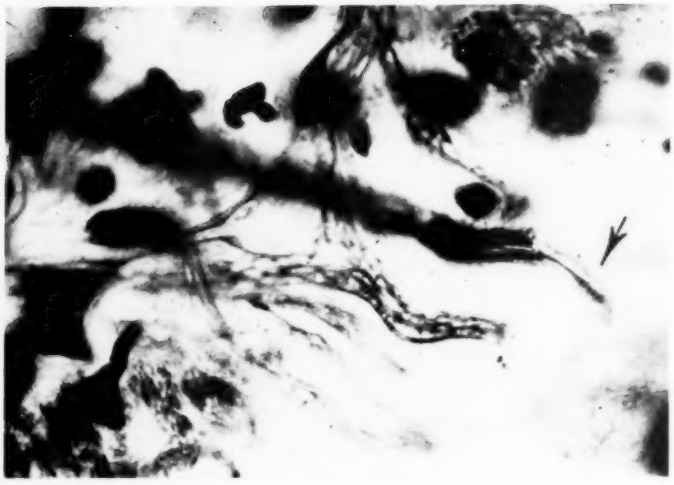

Fig. 1.—A representative portion of the autonomic plexus found in parotid gland adjacent to secretory gland cells. Note the true interlacing fibrils suggesting intimate inter-relationship between individual fibers. A varicosity or bulb-like ending typical of autonomic fibrils is demonstrated (arrow). Gros-Schultze. x 1000.

Schultze[1] and the silver amine complex of Scharenberg.[2] The sections were then placed in 0.2 per cent gold chloride for 10 to 30 minutes, subsequently dehydrated with creosote and then mounted.

Silver impregnation by the Gros-Schultze method has the advantage of staining nerve fibers deep black while the connective tissue in salivary parenchyma remains virtually colorless. The silver amine complex technique was utilized where sensitive impregnation of the finest nerve fibrils and nerve endings was required. However, connective tissue was also moderately stained with the Scharenberg technique.

OBSERVATIONS

Course, Branching and Character of Nerve Fibers. As the nerve fibers enter the gland parenchyma they are closely associated with the interlobar and interlobular ducts and blood vessels. They tend to follow the duct architecture and vascular tree and to subdivide with them. The fibers are mixed medullated and unmedullated, the later

predominating. The greater number of nerve bundles appear to be associated with the excretory ducts rather than with the blood vessels. Isolated branching does occur at the intralobar and intralobular level of duct bifurcation; an individual fiber may separate from a large bundle to pass toward the glandular acini. At the intercalary duct level of bifurcation the smaller nerve fibers may pass between individual acini eventually to end about neighboring acini of the same lobule.

Terminal Branching and Peripheral Neural End-Organs. The terminal reticulum about the individual acinar cells assumes the character of an intimate and fine syncytial network of nerve fibrils. They appear to lie simply against the individual cell wall. Varicosities or bulb-like endings may emanate from these terminal fibrils (Fig. 1). In addition to the fine terminal reticulum seen in both parotid and submaxillary glands, there are corpuscular peripheral neural endings which have an intimate relationship with the salivary ducts and glandular parenchyma. Two varieties are identified in this study:

A) Encapsulated receptor type endings.

B) Autonomic ganglion cells.

Encapsulated Receptor Endings. Three corpuscular sensory endings are identified:

1) Vater-Pacini type (corpuscula lamellosa).[3-5]

2) Meissner type (corpuscula tactus).[6,7]

3) Krause-Ruffini type (corpusculum bulboidum).[8-10]

Vater-Pacini Type. Closely related to the salivary excretory ducts at the lobar and lobular level is an elongated, elliptical formation measuring 15 microns wide and 25 microns long with a thin but definitely lamellated capsule (Fig. 2). There is an *outer bulb* or shell void of nerve structures. The lamellae are concentric and are compressed, but separated from one another by interlamellar spaces containing small capillaries (Fig. 2B). The *inner bulb* or central core contains a whorl-like neurofibrous structure supplied by a medullated axon. Branching of its axon terminates by end-bulbs without apparent intercommunication (Fig. 2A).

Meissner Type. Also in the connective tissue which surrounds the large excretory ducts is another elongated and ellipsoid encapsulated ending which measures 15 microns in length and 25 microns in

Fig. 2.—Vater-Pacini receptor ending in parotid gland. A, longitudinal section. There is a thin but definitely laminated capsule and a central core containing a whorl-like neurofibrous structure supplied by a medullated axon. Gros-Schultze. x 1000. B, cross section demonstrating the thinly laminated capsule and circular arrangement of the neurofibrous central core. Note the close proximity to salivary excretory duct. Gros-Schultze. x 1000.

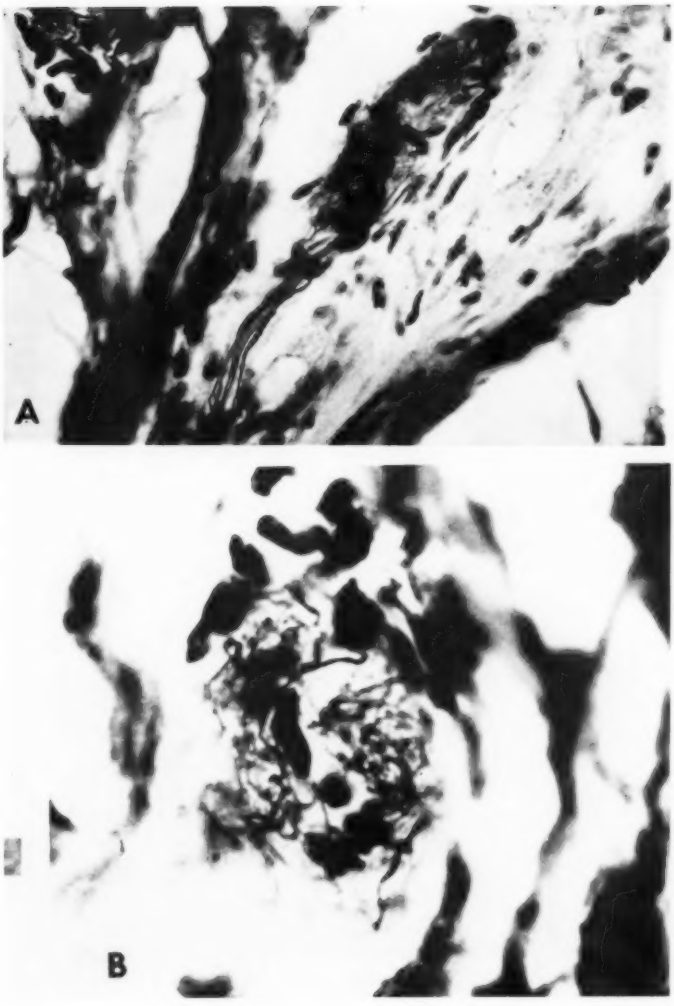

Fig. 3.—Meissner type receptor ending in submaxillary salivary gland. A, longitudinal section shows a thin, unlaminated capsule containing many fine fibrils and branching cells of a fibrocytic variety. Silver amine technique. x 1000. B, a cross section demonstrating the horizontal arrangement of nerve cells and fibers ending in open neurofibrillar networks. Silver amine technique. x 1500.

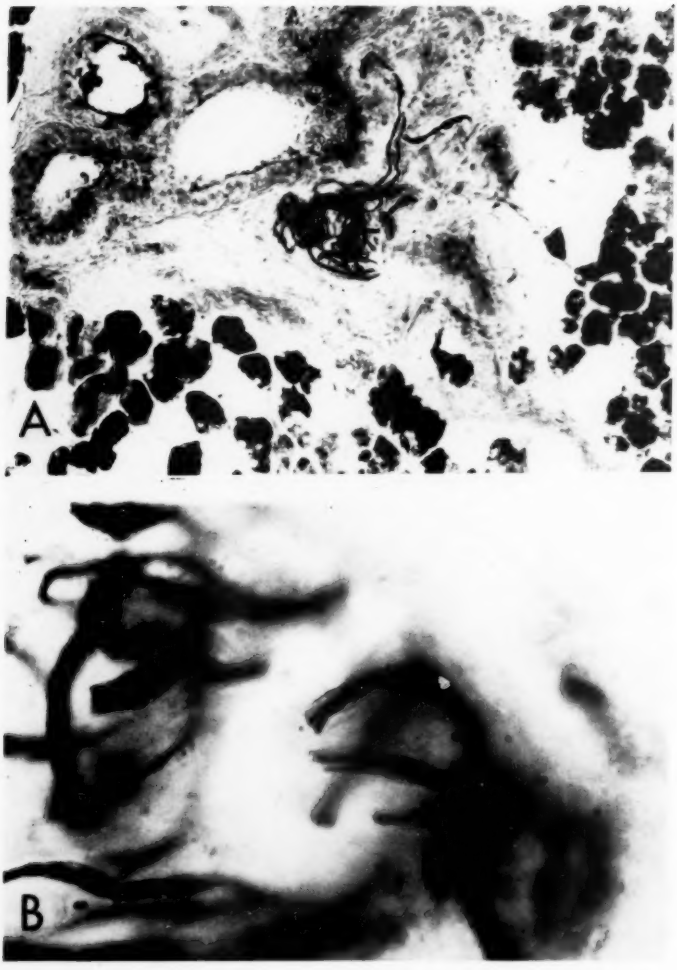

Fig. 4.—Krause-Ruffini type receptor corpuscle in parotid gland. A, the largest of the receptor endings is composed of many short, coiling fibers which appear to end in open neurofibrillar networks. Gros-Schultze. x 250. B, an oil immersion view demonstrates that the coiled fibers appear to end as closely intertwined neurofibrils. Gros-Schultze. x 1500.

width (Fig. 3A). The capsule is very thin, not laminated and contains many fine fibrils and branching cells of a fibrocytic variety. Medullated axons enter the corpuscle, in the interior of which is a horizontal arrangements of nerve fibers and endings (Fig. 3B) which is characteristic of Meissner's corpuscular endings.[7]

Krause-Ruffini Type. A third receptor corpuscle found in the interductal connective tissue is a morphologic cross between a Ruffini and Krause end bulb (Fig. 4A). The capsule is exceedingly thin and the receptor is as large as an excretory salivary duct. It is composed of many short, coiling fibers which appear to end in open or free neurofibrillar networks (Fig. 4B).

Autonomic Ganglion Cells. These ganglion cells are found scattered in the periparenchymal connective tissue of the submaxillary salivary gland exclusively and belong to the parasympathetic system. Figure 5 demonstrates a unipolar parasympathetic ganglion cell with its medullated axon.

A second type of automonic ganglion cell identified is the bipolar parasympathetic ganglion cell with its fusiform body, axis cylinder and single dendrite embracing a portion of a secreting cell of a salivary acinus by a button or bulb-like ending (Fig 6).

COMMENT

Parasympathetic Ganglion Cells. The currently accepted neuroanatomical facts support our observations of absence of preganglionic and postganglionic sympathetic and parasympathetic cell bodies in the parotid gland. The cell bodies of the sympathetic primary or preganglionic fibers are located in the upper thoracic spinal cord whereas the cell bodies of the sympathetic secondary or postganglionic fibers are found in the superior cervical ganglion. The same holds true for the submaxillary salivary gland. All parasympathetic preganglionic cell bodies are located in the salivatory nuclei of the brain stem. Whereas the cell bodies of the postganglionic parasympathetic fibers to the parotid gland are located in the otic ganglion and therefore outside the parotid gland; the cell bodies of parasympathetic postganglionic fibers to the submaxillary gland are located along the excretory ducts in the hilum and within the gland parenchyma as well as in the extraglandular parasympathetic ganglia.

Sensory Endings. Sensory endings in the salivary glands have been described by many investigators. Sasybin illustrated Vater-

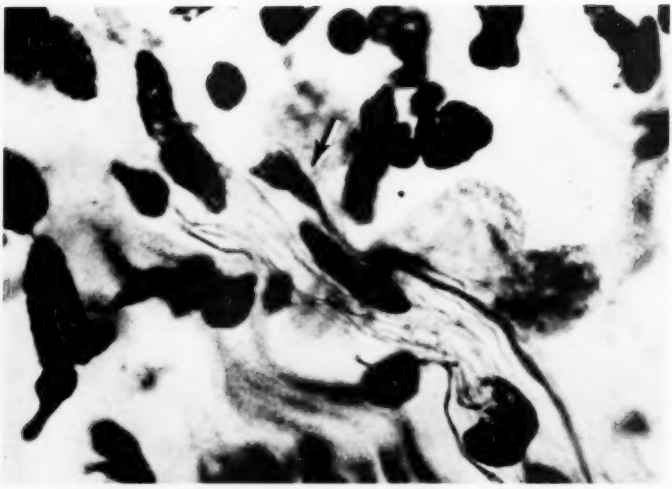

Fig. 5.—A unipolar parasympathetic ganglion cell with its axon accompanying unmedullated fibers in glandular connective tissue of submaxillary salivary gland. The cell body is small (10 microns) and is triangular (arrow). Gros-Schultze. x 1000.

Pacini corpuscles and Krause end bulbs in the human as well as in other animals. This report illustrates three encapsulated receptors or sensory endings: the Vater-Pacini type corpuscle, Meissner type corpuscle and the Krause-Ruffini end-bulb. These receptors are not completely identical with the endings described for human digital, genital and ocular sensory endings. However, they are strikingly similar in morphologic pattern to be considered representative anatomic variants. Consequently they must subserve similar functions. Since most visceral sensations are those of pressure, these corpuscles may be the endings which indicate this visceral sensation. The close application of these structures to the excretory ducts suggests that these organs provide a mechanism for signalling changes in tension of secretion (saliva) flowing through the ducts. A more complete evaluation of the functional significance of these structures must await careful physiological and cytochemical analysis.

Character and Branching of Nerve Fibers. That nerve bundles most frequently follow the salivary ducts, though some may course with blood vessels, is in agreement with other investigators. No histo-

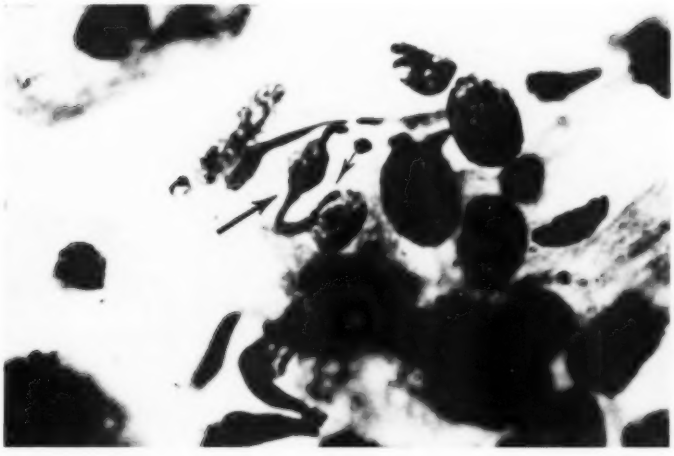

Fig. 6.—A bipolar parasympathetic ganglion cell with one process closely applied to the nucleus of a secreting gland cell. The terminal process appears as a foot plate (arrow). Gros-Schultze. x 1000.

logical difference between nerve fibers following ducts and blood vessels could be discerned in this study. The nerve bundles contain mixed medullated and unmedullated fibers. The medullated fibers are sensory and the unmedullated fibers are sympathetic and parasympathetic postganglionic in type, with the exception of medullated preganglionic parasympathetic fibers in the submaxillary salivary gland.

It has been emphasized that nerve fiber bundles through repeated branching along with the salivary ducts progressively narrow in caliber and eventually terminate as a fine reticulum. The present study, however, agrees with the observation of Berkley[11] wherein individual nerve fibers can separate from the parent nerve bundle considerably proximal to the terminal reticulum.

Terminal Branching. The controversy of a terminal reticulum versus bulb-like endings upon glandular cells has long been cause for debate. Zimmerman[12] presents an excellent summary of opposing views and concludes that all secretory cells of the salivary glands are in direct contact with nerve endings which are simple filamentary free endings, and some authors are in agreement with this concept. As

early as 1888 Retzius[13] demonstrated a fine network of nerve fibrils passing over glandular acini. He described them as a continuous syncytium within the acini. Retzius was of the impression that they ended intracellularly. Arnstein, Sasybin, Huber, Berkley and Champy described and illustrated droplet or bulb-like endings upon secretory cells in salivary glands of several animals. Stormont, working with the rabbit, found endings upon gland cells after sympathetic denervation which were assumed to be parasympathetic in nature. Sasybin, however, found nerve fibers ending in bulbs in salivary glands which had their parasympathetic nerve supply cut. Jalowy, working with the owl, maintained that two types of nerve endings occurred: "the typical intraplasmatic nerve endings in the form of end bulbs and strands of neurofibrils." He felt that these two types of nerve elements were the anatomical expression of antagonistic innervation of the gland cells.

In the present study a fine, filamentary nerve fibril syncytium as well as bulb-like endings were found in both parotid and submaxillary salivary gland tissue. We found that the terminal syncytial reticulum is more abundant in the parotid, an albuminous or serous secreting salivary gland, and less abundant in the submaxillary salivary gland, a mixed serous and mucous secreting gland.

The controversy concerning the true nature of the filamentary syncytium has reached an impasse because of the limited resolving power of the light microscope. Thus we do not really know if there is a meshwork of individual fibers which will end in individual cells, whether these fibers or even bulb-like endings lie against the cell membrane or whether they actually penetrate the cell. This and further detailed information will need to be obtained by studies utilizing the electron microscope which, because of its higher resolving power and greater sensitivity to differences in density may be expected to yield much toward solution of these problems.

SUMMARY AND CONCLUSIONS

Study of sections of human parotid and submaxillary salivary glands, stained by the Gros-Schultze and new silver amine complex techniques resulted in identification of corpuscular nerve endings and filamentary nerve fibrils not previously demonstrated by photomicrography.

As nerve bundles enter the salivary gland parenchyma, they tend to follow the duct architecture and to subdivide with the ducts. Single nerve fibers may separate from a large nerve trunk. Repeated

subdivision of nerve bundles may be the pattern, but not exclusively so in the formation of the terminal neural network.

Terminal relationships between the glandular cells and their innervation may be either through a syncytium of fine nerve fibrils or by bulb-like endings upon the cells. The latter situation occurs with greater frequency in the submaxillary salivary gland.

Because of the limitations of the resolving power of the light microscope, it is not known if the terminal reticulum or bulb-like endings lie against the cell wall of the secretory cells or whether they actually penetrate the cell.

Three types of modified corpuscular sensory endings are demonstrated in both parotid and submaxillary salivary tissue: the Vater-Pacini type, Meissner type corpuscule and Krause-Ruffini end bulb. They appear to be pressure receptors.

Unipolar and bipolar parasympathetic postganglionic fibers with their cell bodies are demonstrated in submaxillary salivary gland exclusively. This is in accordance with the accepted neuroanatomical fact that ganglion cell bodies associated with the parotid gland are extraglandular.

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ACKNOWLEDGEMENT. The authors are grateful to Dr. Elizabeth C. Crosby, Professor of Anatomy and to Dr. K. Scharenberg, Professor of Neuropathology, University of Michigan, for valuable service in this study.

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The Scientific Papers of the American Laryngological Association

XXXIV

THE DOCTOR'S RESPONSIBILITY TO HIS PATIENT

PRESIDENTIAL ADDRESS

WILLIAM J. MCNALLY, M.D.

MONTREAL, CANADA

SCIENCE AND EDUCATION

In this age in which we are living we hear on all sides the need for education and especially for scientific education and research. The space program race is on and our educational system has been considered lacking. It has been shown that there is a shortage of scientifically trained personnel. This has resulted in a panic reaction in a large section of the country. The achievements of the Soviets were first minimized and then exaggerated—there has been a certain loss of sense of proportion. After more sober thought it has been realized that though we are short of technically trained people, it is even more essential that we have people who are trained to think and that they must be able to think clearly. The prime purpose of a university is to teach us how to assess the ideas with which we are confronted—to develop prudence and wisdom.

The following is taken from the Book of Wisdom, chapter 7, verses 7 to 14.

> I prayed and Prudence was given me; I pleaded, and the spirit of Wisdom came to me. I preferred her to sceptre and throne and deemed riches nothing in comparison to her. Nor did I liken any precious gems to her; because all gold, in view of her, is a little sand, and before her, silver is to be accounted as mire.

A leading article in the British Medical Journal of September 3rd, 1949, page 520, includes the following.

"The training in scientific method, whilst providing the student with capacity for logical, impersonal, objective thought, should add point to the skill with which he applies his treatment and to the understanding and fellow feeling that soften his conversation with his patient."

Some progress has been made especially in radio, television, radar, etc. The moon can now be used for the reflection of messages to communicate with faraway places. By reflecting radar off the planet Venus more accurate information can be determined about interplanetary distances, etc.

As a by-product of all these studies, medicine benefits from improvements in technique and equipment (radioactive isotopes, for example) as well as from increased knowledge about bodily functions and resistances under novel and "unearthly" conditions.

RESEARCH

It is now generally recognized that research is an essential part of medical practice and progress. In most of the special fields of medicine research is a fundamental part of the training. This is especially true of some of the newer specialties such as neurosurgery and psychiatry and the cardiorespiratory divisions. The major specialties of medicine and surgery have insisted upon research training in their programs.

Most of us in this Association are otorhinolaryngologists and I fear we must admit that research has, with a few outstanding exceptions, made its greatest strides in otology.

There is experimentation in progress which is concerned with respiration, with speech, with taste and smell, etc., but it has largely been carried out by physiologists, anatomists and neurophysiologists, and there are all too few rhinolaryngologists involved.

EXPERIMENTAL PROCEDURES ON PATIENTS

In the basic sciences allied to our specialty research is carried out in large part through animal experimentaion. In some cases, however,

patients or normal human subjects are the experimental animals. In clinical research, on the other hand, the patient is very frequently directly involved in the experiment though many problems can be solved at least in part by animal experimentation or by study on the cadaver.

Clinical research can take many forms and may be very involved. As Walshe said, it is Nature that sets up the experiment. We must determine what is the stimulus and where it is acting.

There are some special problems which can be solved only by an experiment carried out on the patient with his full knowledge and consent. This is especially true when the patient's conscious co-operation is a necessary part of the experiment.

Medicine is an experimental science—every differential diagnosis implies some degree of experimentation, as do many of our everyday routine treatments. The matter of morality is not a problem for the doctor whose guiding principle is his patient's well-being. However, we must guard against the temptations and dangers of too big a practice. It can happen almost imperceptibly

a) that we find ourselves not giving each patient the careful and complete examination he requires,

b) that we are having patients back for an extra visit in order to meet the rising overhead,

c) that we are condoning treatments on a wholesale scale by an assistant (sometimes non-medical) not carefully supervised,

d) that we are thinking of the patient as one of a series, and lose sight of his rights as an individual,

e) that we are falsifying insurance and other documents for the patient's or for our own benefit,

f) that we are recommending operations when the indication is not solely for the good of the patient.

These are some of the immoral practices which are all too widespread and which are contributing to a loss of the physician's former

exalted place in the community, and are ammunition for those advocating State Medicine.

We are not considering here the morality of any do or die procedures adopted by the doctor when confronted with terminal illness. We are much concerned with the morality of those experimental procedures carried out on patients for the amelioration or cure of a disease which is not completely incapacitating or lethal though it may be a handicap.

Before considering the many problems which arise in connection with experimentation on patients we might recall a passage from the prayer of Maimonides.

> "Inspire in me a love for my art and for Thy creatures. Let no thirst for profit or seeking for renown or admiration take away from my calling. Keep within me strength of body and soul, ever ready, with cheerfulness, to help and succor rich and poor."

And we might add, let us remember that Christ said, "As long as you do it unto one of the least of these My brethren, you do it for Me."

RESULTS OF EXPERIMENTATION ON THE PATIENT

When medical research is carried out on its immediate object, living man, it is to be hoped that the interests of science, of the patient, and those of the community will be served. Under such circumstances one cannot insist that all danger and risk be excluded. The weighing of the dangers and the advantages must be left to the experienced, competent and conscientious doctor.

A doctor must resist the temptation to do an experimental operation on a patient before he has subjected his idea to sufficient animal experimentation, especially if it is partly with a view to speeding up results or in order to get prior credit for a certain technique. This is particularly true when experimentation on animals closely allied to man would give many of the answers, as for instance where impaired parts of the body are replaced or reinforced by plastic implants. The long term behavior of such an implant and its possible effects on adjacent important parts of the body can be determined before a patient is exposed.

ETHICAL RULES OF THE AMERICAN MEDICAL ASSOCIATION

To conform to the requirements of the Americal Medical Association with regard to the carrying out of experimental procedures on a patient, three conditions must be satisfied. These are as follows:

1) The voluntary consent of the patient on whom the experiment is to be performed, must be obtained.

2) The danger of each experiment must be previously investigated by animal experimentation.

3) The experiment must be performed under proper medical protection and management.

THE PATIENT'S CONSENT

The patient's consent is the responsibility of the doctor. First of all it presumes that the doctor has given the patient all the information possible to decide whether or not he will consent to the procedure. This means that the doctor must acquaint the patient with both the immediate and long term possible complications and risks and it implies that no pertinent information will be withheld. It also presumes that the patient will be told of other possible procedures and treatments with their relative chances of success and their risks.

The patient is often impatient of infirmity and in his anxiety to be better is over-optimistic. The surgeon must not take undue advantage of this.

The patient or his guardian must be able, by virtue of his circumstances, of his nationality and of education, etc., to comprehend the various possibilities so that he may give an enlightened consent. If he is not, then an added moral responsibility is placed upon the doctor.

The only rights which the doctor has over the patient are those conferred upon him by the patient.

THE DOCTOR-PATIENT RELATIONSHIP

Through the years the profession has won the confidence of the patient. He has been led to assume that his doctor would not propose

a treatment which had not been fully tried or one which was not likely to have a reasonable chance of success. As doctors we must be fully conscious of our responsibilities. The golden rule applies—if you would not submit to the operation yourself or have it performed on your child then you are not at liberty to offer it to the least consequential patient.

Guttentag has said, "The physician-patient relationship is the justification of our profession—one human being is in distress, in need crying for help; and another fellow human being is concerned and wants to assist him."

To recommend or perform an experimental operation or treatment on a patient without adequate prior animal experimentation when possible or without full explanation of the risks involved are crimes which jeopardize the proper doctor-patient relationships of the whole profession.

Instead of speeding up results such practices are more likely to impede progress since most advances are based upon many preceding contributions. Great care must be exercised not to be responsible for a half-truth, for a misconception, or for poorly supported statements getting into the literature.

It is a crime for a doctor to betray the implicit trust placed in him by his patient. It is a greater crime than the dishonesty of payola or of the quiz programs with their associated perjury or of the ghost writing of academic theses. It is more akin to armed robbery because even if there is not the intent to kill, there is at least the readiness to maim; and it is even worse because the doctor is exposing to unnecessary risk or damage or destruction the well-being of a friend—a fellow man who has placed his implicit and childlike trust in him.

This responsibility can be shrugged off by saying the patient consented—but did he really know to what he had consented? This is particularly true when the treatment is elective and not a matter of imminent life or death. If the physician forsakes the golden rule his actions are in line with the present day deterioration in public morality. Guttentag warns us that "we must be alert with ourselves lest in our zeal for truth, we create healthy bodies at the cost of 'our own' morally dull minds."

SCIENTIFIC KNOWLEDGE

Christianity is well aware that the acquisition of new truths or the confirmation of accepted truths is a good which must be encouraged. However, we must be on our guard that the methods used are not likely to infringe on the rights of others. The mere fact that a certain method may yield results of scientific value does not establish it as necessarily licit. The personal right of the patient to the life of his body and soul is a value superior to that of scientific knowledge.

At a symposium of the medical staff of the University of California School of Medicine in San Francisco, discussing the problem of experimentation on human beings, Michael B. Shimkin has this to say:

> "The complex problems of the use of human subjects in medical research involves many supra-scientific considerations. The application of the guiding principles to specific experimental situations, however, will always be open to individual interpretations and differences. Science per se is neither moral or immoral; it becomes moral or immoral only as moral or immoral human beings use its powerful techniques."

PATIENTS' RIGHTS

Christian ethics points out that man is not absolute master of his body or of his soul. He has the right of use limited by the natural finality of his human nature. Since he is a user and not a proprietor his right to destroy or to permit the doctor to destroy any part of his body is limited.

According to the principle of totality and by virtue of his right to use the services of his body as a whole, the patient can allow a certain part to be removed if it is interfering with the health of the body generally. On the other hand, a patient cannot consent to an operation when it is reasonably sure that such an operation will deprive him of his higher faculties. The part exists for the good of the whole and may be disposed of under certain circumstances. Before applying the principle of totality it must be established that the object is in the relation of a whole to its parts. For example, is it on the level of essence or merely on that of action? Does it apply to the part in all its relations? Does it absorb the part completely or does the part have a limited independence? For example, a hand removed has by its own nature no finality or independence.

O'Donnell discusses the difference between absolute ownership over himself, which the individual does not possess, rather than wise administration which is licit. He points out that wise administration does not permit an individual to submit to a dangerous experiment. The objective probability of incurring some evil—if it would be judged to be a considerable risk by a group of ordinary individuals, if they have been placed in possession of the facts, would take the experimental act out of the realm of wise administration and place it in the category of ownership.

The State recognizes these limitations of an individual's rights over himself and considers it a crime for him to take his own life.

THE COMMON GOOD

We must beware of the fact that the community only exists for man. It is not a physical unity existing in itself and its members are merely collaborating for the common good. Man, on the other hand, has a unity subsisting in himself—any one part of his body cannot subsist by itself.

Government can make demands upon a citizen but it may not interfere with his physical being. Pius XII explains that

> "When there is a question of the execution of a condemned man, the State does not dispose of the individual's right to life. In this case it is reserved to the public power to deprive the condemned person of the enjoyment of life in expiation of his crime when by his crime he has already disposed himself of his right to live."

The Nuremberg trials brought out many instances where the State transgressed on the above principles and shocked the civilized world by handing over its citizens as research subjects in the name of the common good and the advancement of science.

At the symposium of the California School of Medicine, San Francisco, already referred to, the broad problem of experimentation on human beings was discussed in some of its various aspects and was reported in *Science*. Great stress was laid upon the dignity of the individual and on the fact that he has inalienable rights that supersede any consideration of science or general public welfare. Before any experiment could be carried out on a patient they also endorsed

the three provisos of the American Medical Association already listed plus the two following:

a) the sound hope of fruitful results but with due proportion between this and the risks involved,

b) avoidance of any experiment when there is *a priori* reason to believe that death or a disabling injury will occur.

SUMMARY AND CONCLUSIONS

I am sure that we are all agreed that the promotion of research is a fundamental function of our Association—the Association has funds set up for the encouragement of research.

Our annual scientific program should be designed to encourage research in its membership in addition to maintaining a high level of clinical performance.

Research training and productivity should be factors in the selection of new Fellows.

Our educational approach to research and experiment should tend to develop conceptual thinking in the student doctor and must also develop and expand his sense of moral responsibility in order that he may respect the rights of each individual patient.

As physicians we might ask ourselves:

1) Has the treatment which is proposed actually been subjected to sufficient and prolonged animal tests to know, not only its immediate effects but its probable long term results.

2) Is the condition from which the patient is suffering serious enough to justify the risk of total or partial destruction of the part under consideration.

3) Is there no other possible and less dangerous procedure with a prognosis nearly as good.

4) Has the patient been given a true picture of the possible dangers to which his consent exposes him.

5) Has the patient really understood the dangers involved.

6) Am I, the doctor, before God, prepared to assume the responsibility for the result as though I were the guardian of a minor patient and as though that patient were my own child?

The doctor must take great care to do nothing which will undermine the traditional role of the physician as the helper and friend of each individual sick man. He must retain the utmost concern for the welfare of the individual patient and must avoid the danger of thinking of the patient as only one in a long series in which he is getting a certain percentage of good results.

The doctor has only those rights which are conferred upon him through the enlightened consent of the patient or his guardian.

The patient may not confer unlimited rights which he does not possess—he does not have the absolute ownership of his body but only the right of use.

I should like to conclude with the following quotation from Pius XII:

"The great moral demands force the impetuous flow of human thought and will to flow, like water from the mountains, into certain channels. They contain the flow to increase its efficiency and usefulness. They dam it so that it does not overflow and cause ravages that can never be compensated for by the special good it seeks. In appearance moral demands are a brake. In fact they contribute to the best and most beautiful of what man has produced, for science, the individual, and the community.

May God Almighty in His benevolent providence give us His Blessing and grace to this end."

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XXXV

PHYSIOLOGY OF OLFACTION AND GUSTATION

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The chemoreceptors are among the first of the major sensory receptors to develop in the evolutionary sequence. In lower animal forms, they are intimately related to the major tasks of the animal such as mating, food searching, food selection and self preservation. It was shown by Richter[6] many years ago that lower mammals such as rats can select foods to maintain a balanced diet. Furthermore, if a salt or vitamin deficiency is present in the animal, the preference threshold to the needed substance will decrease and the animal will increase its uptake of the necessary food to overcome the deficiency. For example, an adrenalectomized rat shows preference for salt at very low concentrations and governs his diet accordingly.

Modern man lives in a world with a large variety of foods, so that self selection of food for bodily protection is seldom necessary. The ability to use chemoreceptors for this purpose when necessary, however, is shown by the fact that diet selection is sometimes made during certain diseases. Men living under primitive conditions also have highly developed senses of taste and odor.

GUSTATION

The function of the taste and olfactory receptors is to monitor the food intake and the air breathed. Receptors for the olfactory, visual and auditory senses are well protected, but those of the gustatory must be readily accessible to test food taken into the mouth. For this reason, other protective mechanisms have been developed for the sense of taste. For example, if the taste nerve is injured, the

This research was supported in part by grants from the National Institute of Health and the Office of Naval Research.

taste buds degenerate but reappear once again when the regenerated nerve arrives at the surface of the tongue. There is no similar receptor regeneration known for other major sense organs. Taste cell precursers continually undergo mitotic division so that each cell within the taste bud may be replaced. Another protective mechanism is afforded by the fact that several different nerves carry gustatory information. The chorda tympani nerves innervate the taste buds of anterior two-thirds of the tongue, whereas the glossopharyngeals innervate those of the posterior third of the tongue. Dual innervation protects taste function after injury to any one nerve bundle.

The anatomy of the taste receptors will not be considered here. There are three ways to study the function of taste receptors. First, taste sensations of humans may be analyzed by psychophysical methods. Second, the behavior of animals may be studied in the presence of various chemical stimuli. Third, electrical activity of the nervous system of experimental animals may be studied in response to chemical stimuli presented to the tongue of anesthetized animals. It may be mentioned that the latter method might also be applied to humans by recording from the chorda tympani nerve in the middle ear while various solutions are flowed over the surface of the tongue. The results of electrophysiological investigations of taste will be stressed in this paper.

METHOD

The animal is anesthetized with urethane or nembutal and the chorda tympani dissected free from surrounding tissue. The peripheral end of the nerve bundle is lifted on to a metal electrode. Another indifferent electrode is placed near the nerve. A flow chamber is placed over the tongue so that solutions can be continually flowed over the same area (Fig. 1).

RESULTS

Little neural activity is recorded from a rat when water is used as a stimulus. If sodium chloride, for example, is flowed over the surface of the tongue, a response is observed within 100 msec. Diffusion contributes little to this latency; accordingly most of the delay in response is due to processes in the taste cell itself. The response to sodium chloride approaches a steady state value within a few

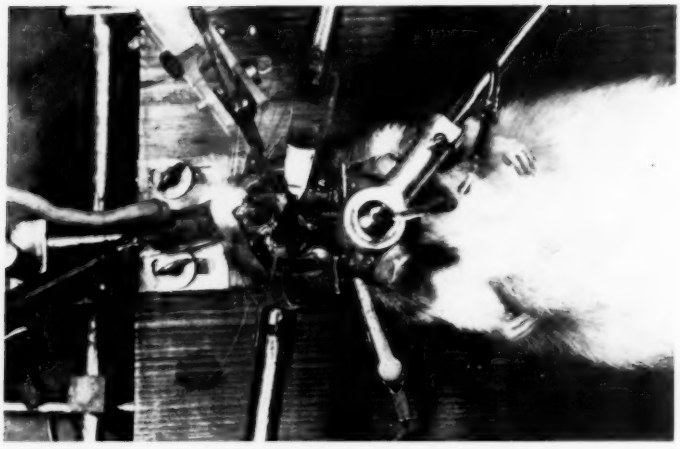

Fig. 1.—Ventral view of rat taste preparation. Notice the flow chamber with the tongue inserted. Two movable electrodes record the neural activity from the dissected taste nerve. This type of preparation may function for 30 hours with taste solutions applied to the tongue once a minute. (Photo by I. Y. Fishman)

seconds and maintains this magnitude for the duration of the stimulus. Thus, little adaptation occurs at the level of the taste receptors after the first few seconds. Since it is well known that the behavioral response of man to a similar stimulus rapidly adapts, this adaptation may be attributed to central and not peripheral neural processes. The stimulating efficiencies of a group of substances may be compared by using equimolar solutions, that is, solutions having the same number of molecules per unit volume of solvent. In such an experiment, the rat responds very well to sodium chloride and rather poorly to potassium chloride. However, other species of animals, such as carnivores, may respond well to potassium chloride and poorly to sodium chloride (Table I). The response of different animals also varies considerably with sweet substances. For example, the guinea pig and hamster respond very well to sucrose whereas the cat responds very poorly and the rat produces a moderate response.[5] This is a positive proof that there is considerable variation in the response to taste stimuli from one species of animal to another.

TABLE I

	RELATIVE TASTE RESPONSE $\frac{NA}{K}$
Carnivores	
Raccoon	0.75
Cat	0.67
Dog	0.43
Average	0.62
Rodents	
Rat	2.0
Hamster	2.8
Guinea Pig	2.6
Average	2.5

In order to study the mechanism of taste stimulation, it is useful to know the magnitude of response to a series of solutions of different concentrations of the same chemical. This may easily be found by recording the neural activity to a given concentration of stimulus, summating electronically and displaying the result on a Sanborn recorder. With this procedure, the height of the response is directly proportional to the magnitude of neural activity. The magnitude of response increases with concentration until a level of saturation is reached as shown in Figure 2.

What is the mechanism by which the chemical stimulates a taste receptor? One may assume that the atom or molecule simply is adsorbed to the surface of the taste cell, probably to the taste 'hairs'.[2] This reaction can be written as $A + B = AB$. One may assign the value N to the total number of sites to which the particular chemical can be adsorbed on the surface of the taste cells. The number of these sites filled at any concentration, C, of stimulus can be assigned the value Z. From elementary chemistry, the equilibrium constant K of this reaction is the concentration on the right hand side divided by

Fig. 2.—Summated electrical response of chorda tympani nerve of rat to NaCl solutions flowed over the surface of the tongue. Concentrations are 0.005M, 0.01M, 0.025M, 0.05M, 0.10M, 0.25M, 0.50M, 1.0M. Test solutions of 7 to 10 seconds duration of applications are interspaced with water rinses. One large division equals 20 seconds.

the product of the concentrations on the left hand side of the equation, or

$$K = \frac{Z}{C(N\text{-}Z)}$$

where C is the concentration of the stimulus, A, and (N-Z) the number of unfilled sites. It is impossible for us to know the numerical value for the number of sites available or the number of sites filled. However, if the magnitude of response is directly proportional to the number of sites filled ($R = aZ$), and if the maximum response obtained at high concentration of stimulus occurs when all sites are filled ($Rs = aN$), then the above equation becomes

$$\frac{C}{R} = \frac{C}{Rs} + \frac{1}{KRs}$$

where R is the magnitude of response to taste stimulus of concentration C and Rs is the maximum response available at high stimulus concentrations. This has been called the fundamental taste equation which relates the magnitude of response to the concentration of the stimulus. The only unknown in this equation is the equilibrium constant, K, which can easily be found if the magnitude of response to

two different concentrations of the stimulus is measured. The equilibrium constant has great theoretical significance to the physical chemist. When calculated, one finds that this constant is very small, meaning that the forces binding the chemical stimulus to the taste cells are very weak. This seems reasonable, since the adsorbed molecules can easily be washed off with a water rinse.

No enzymatic reactions are involved in this first step of taste receptor stimulation. The magnitude of response to salt solutions is independent of the temperature of the solution over a 15°C range and the response is also independent of hydrogen ion concentration from pH3 to pH11. After the molecules are adsorbed to the surface, the taste cell depolarizes. That is, most cells at rest have a difference of electrical charge between their interiors and exteriors. This difference in charge changes when a sensory cell is stimulated. Such is also the case for the taste cell as measured with microelectrodes inserted into single taste cells. These changes are the order of magnitude of 5-30 millivolts and initiate the nerve action potentials.

It is commonly believed that there are four fundamental taste qualities; salty, sour, bitter and sweet, from which all other tastes can be derived.[1] This certainly is an oversimplification of the sense of taste, but the generalization can be considered accurate when studying some of the simpler functions of taste. The evidence for four taste qualities comes from several sources. First, not all areas of the tongue respond to a given substance in the same manner. For example, the sweet tastes are better perceived near the tip of the tongue, whereas the bitter are better perceived near the posterior of the tongue. Second, many complex tastes may be duplicated by the proper mixing of various quantities of substances representing the four taste qualities. Third, certain drugs, such as the juice from Gymnema leaves, applied to the surface of the tongue, decrease the intensity of one taste quality without affecting the other three. Fourth, the neural activity from single taste nerve fibers may be recorded in response to various chemical stimuli. These fibers have been grouped according to their ability to respond to one or more of the four taste qualities.[5] Thus some fibers respond only to acids, others only to acids and salts, others to acids, salts, and sugars, etc. Does a single taste cell respond to but one of the four taste qualities or more than one? In order to answer this, microelectrodes were placed in the single taste cells and the electrical response measured to

various stimuli. It is concluded that most taste cells may respond to more than one of the four taste qualities.

Individuals differ in their sensitivity to a number of taste substances. Some of these differences have a genetic origin, as is the case with phenylthiourea (PTC). About thirty per cent of Americans do not perceive the bitter taste of dilute solutions of PTC, whereas the other seventy per cent maintain that the solution is extremely bitter. These differences in sensitivities to taste stimuli may well account for the differences in taste likes and dislikes among individuals of a population. There is also evidence that these likes and dislikes may change with certain diseases or changes in the internal environment of the body. Changes with pregnancy are well known, as are changes in sweet sensitivity in diabetics, certain bitter sensitivities in hyperthyroids, and increased salt sensitivity in people with adrenal deficiency.

Taste is quite dependent upon the chemical structure of the stimulating substance. For example, orthotolylurea is tasteless, whereas metatolylurea is bitter, and paratolylurea is sweet. Stereoisomers may also have different tastes. These observations suggest that the reaction of the taste substance to the cell surface is dependent upon the configuration and orientation of all the molecules involved.

OLFACTION

The olfactory sense differs greatly from that of the gustatory. Man can differentiate thousands of different odors at concentrations as much as a million times more dilute than those normally used in gustation. The olfactory receptors also differ greatly from the taste receptors. The former are bipolar neurons and not differentiated epithelia cells. The dendritic processes of these neurons may be stimulated by odors carried to the receptive area in a gaseous stream. There are about 100,000,000 of these receptors in the rabbit in contrast to less than about 5000 taste receptors in the same animal. The functional significance of this large number of receptors is not known, but it may be related to odor quality discrimination. The details of the receptor morphology will be discussed by Dr. DeLorenzo in the following paper, and will not be further considered at the present time.

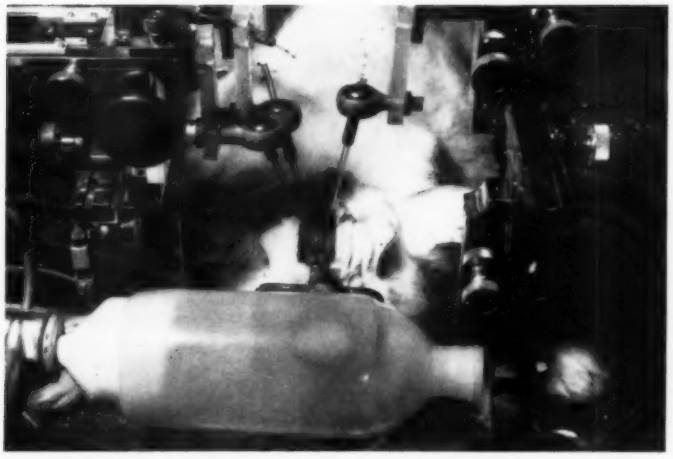

Fig. 3.—Rabbit olfactory preparation. Nerve recording equipment and breathing chamber are shown.

METHOD

The small size of the olfactory nerve fibers (0.2 micron diameter) makes electrical recording from them very difficult. However, it is possible to dissect out a small twig of an olfactory nerve bundle as it passes through the cribriform plate and record from it in the anesthetized rabbit. A small branch of the ethmoidal nerve containing trigeminal sensory fibers can also be placed upon recording electrodes. The nose of the rabbit is placed into a flow chamber (Fig. 3) and an odor of a given concentration is flowed by the nares. The electrical activity is displayed on an oscilloscope or summated and displayed on a Sanborn recorder.

RESULTS

When purified air is presented to the animal, a small amount of spontaneous activity is recorded from the olfactory nerve fibers. During the inspiration of an odor, a large amount of neural activity appears but declines during each expiration (Fig. 4). The magnitude

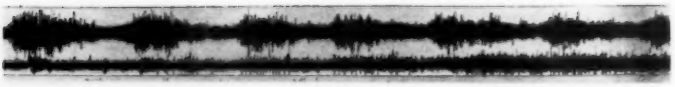

Fig. 4.—Olfactory (upper trace) and trigeminal (lower trace) nerve activity in response to 31 μM amyl acetate inspired once per second by rabbit.

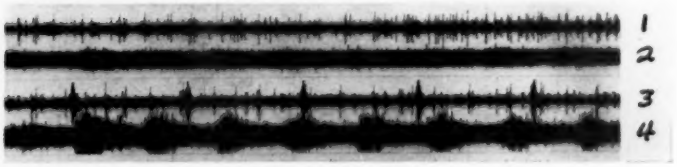

Fig. 5.—Response of rabbit olfactory nerve to orange odor before (Trace 2) and after (Trace 4) 30/min electrical stimulation of cervical sympathetic nerve. Traces 1 and 3 show ethmoidal nerve activity before and after electrical stimulation.

of this electrical neural activity during each inspiration increases with the concentration of the stimulus until a level of saturation is obtained (Beidler, 1958). The threshold of a rabbit to an odor such as amyl acetate is of the same order of magnitude as that observed psychophysically in man. Different odors of equal concentration initiate different magnitudes of neural response. At the present time it is not possible to record from a single olfactory nerve fiber and therefore we have little information concerning the ability of a single receptor to respond to different types of odors.

The magnitudes of the neural responses to successive inspirations of a low concentration of odor remain constant. At high concentrations of odor the neural magnitude declines with successive inspirations. Adaptation to some odors is complete such that no neural activity is recorded after several seconds of stimulation. Other adaptive processes occur in the olfactory bulb even at low odor concentrations so that the olfactory response quickly adapts after it is presented to an observer.

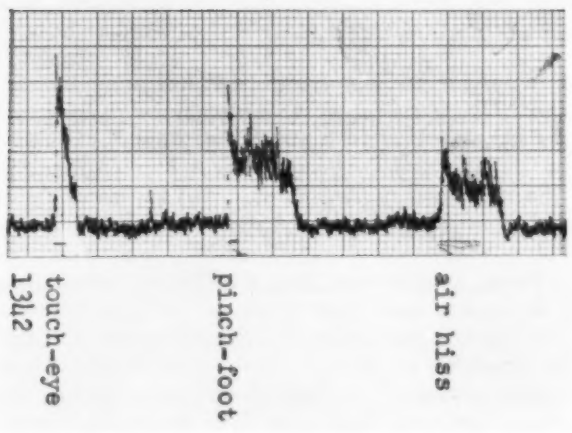

Fig. 6.—Summated electrical activity of ethmoidal nerve in response to stimulation of eye, foot and ear with appropriate stimuli. One large unit on the time scale equals 20 seconds.

Well controlled experiments with animals under normal breathing conditions are difficult to obtain, since the odor stimulus initiates reflexes which result in a change of rate and depth of inspiration. These in turn change the intensity of response. To overcome this obstacle, the trachea of the animal may be cannulated and the odor drawn through the nares by a syringe attached to the trachea. In such experiments adaptation occurs rapidly and may go to completion at high concentrations. If the magnitude of odor stimulus is abruptly increased, the neural activity will also immediately increase, but will decline within two seconds to a new steady state level. Conversely, if the odor concentration is suddenly decreased, the neural response immediately decreases and then rises slightly to a new steady level lower than the initial level.

The response of the olfactory receptors is also dependent upon the rate of flow of the odor through the nares. If the trachea is cannulated, the response to a low odor concentration passed through the nares will increase with the flow rate until it attains a value of 1-4

liters/minute. If a small polyethylene cannula is inserted into the nares and pushed up to the olfactory area so that the odor flows immediately over the epithelium, a maximum response to an odor is obtained when the flow rate is about 2 cc/second.

The trigeminal nerve innervates the olfactory region as well as many other areas of the nose. It is commonly thought that these bare nerve endings are excited only by very noxious stimuli such as ammonia. In order to determine whether this is true, electrical activities of the trigeminal nerve and the olfactory nerve are recorded simultaneously in response to various types of odor stimuli. Mild odors such as phenylethyl alcohol may actually stimulate the trigeminal nerves at lower concentration than the olfactory, even though the smell of the odor to man is not obnoxious. On the other hand, the odor of amyl acetate may excite the olfactory receptors at lower concentration than that of the trigeminal. The trigeminal response is more sluggish, so that the response slowly builds up to a maximum level and tends to remain at this level from one inspiration to the next without an appreciable decrease during such expiration (Fig. 4). One might conclude that the trigeminal nerve serves as an yet unknown function at low as well as high odor concentrations.

Since the magnitude of odor response is proportional to flow rate, it is not surprising that the response changes with nasal vasoconstriction. Upon electrical stimulation of the sympathetic nerve in the neck of the animal, the air passages of the rabbit increase in diameter. This results in an increase in the flow rate of the odor to the olfactory area and thus an increase in the magnitude of response of the olfactory receptors (Fig. 5). It is not known whether all this increase in sensitivity is due to the increased flow rate alone, or whether the sympathetic activity has a more direct effect on the response of the receptors, similar to that observed in other sensory systems. Sympathetic activity is supplied to the olfactory area by way of the ethmoidal nerve. The electrical activity recorded from this nerve greatly increases when the anesthetized animal's toe is pinched, a light is shown on the eye, or a noise made (Fig. 6). Concurrent with this is an increase in olfactory sensitivity to odors. In fact, a moderate concentration of odor may initiate an increase in sympathetic activity to the olfactory region, which in turn results in greater sensitivity of the olfactory receptors. Such reflexes are of great use to an animal since the olfactory sensitivity would be enhanced during times of stress,

such as when a strange sound is heard or an enemy observed. Little is known concerning the basic mechanisms involved in olfactory receptor stimulation. As better methods are developed to record from the olfactory receptors, a greater understanding of the olfactory processes will be obtained.

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Much of the olfactory data was supplied by my co-worker, Don Tucker.

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XXXVI

ELECTRON MICROSCOPY OF THE OLFACTORY AND GUSTATORY PATHWAYS

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The olfactory epithelium and taste buds of mammals are quite simple in appearance when they are fixed and stained with the conventional methods and examined in the light microscope. These tissues consist, essentially, of a specialized receptor cell (the olfactory or the gustatory cell) supported by a second kind of cell, the sustentacular cell. In spite of the fact that the literature is filled with early descriptions of the chemo-receptors of smell and taste, dating from the middle of the 19th century, the present day cytologist has not paid a great deal of attention to these most interesting receptor cells. Some of the general points of interest concerning these tissues require enumeration. First, the olfactory receptors in spite of their rather simple organization and single type of receptor element are capable of rather remarkable fine sensory discriminations. Electrophysiological investigations have led several investigators to suggest that discrimination depends upon the existence of different types of olfactory receptors and that these different types of receptors have selected sensitivities to specific basic odors. Moreover, Ottoson[12] recently suggested that fine differentiation seems to depend upon specific sensitivity of individual receptors to particular molecular configurations. These observations pose the question whether olfactory receptors exhibit morphological differences that correspond to these functional responses. Likewise, the gustatory receptors are most interesting. The taste buds were described by Schwalbe[13] and Heidenhain[11] in the 19th century but despite these early descriptions a great deal of controversy still exists concerning the cytology of the taste buds, the number of cell types

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Supported in part by Grants B-2173 and B-2182 from the United States Public Health Service, National Institutes of Health and the Alfred P. Sloan Foundation.

and the structure of the taste pore.[5] In addition, the functional studies of Pfaffman[10] and Beidler[1] suggest a high order of discrimination in the gustatory receptors as well. Of particular interest to the morphologist is the fact that the taste buds undergo degeneration following interruption of their nerve supplies, and suturing the sectioned gustatory nerves results in taste bud regeneration.[5] Thus, this pathway offers a unique area in which to study both the mechanism of the taste bud excitation or chemo-reception and basic problems of nerve degeneration and regeneration.

ELECTRON MICROSCOPY

The Olfactory System. Figure 1 is an electron-micrograph of the apical tip of the olfactory epithelium obtained from young rabbits 2 months of age. Adult rabbits have chronic rhinitis so young rabbits were employed in this study. The pale process labeled (OR) is the olfactory receptor extending beyond the limiting apical boundary of the olfactory epithelium. Seen extending from its apical portions are numerous cilia arranged in a sepal-like fashion. These cilia are identical in fine structure to cilia seen in other tissues. The olfactory receptor is bounded on all sides by darker, denser cells, the sustentacular cells. Only the very tip of the receptor is thus unsheathed and constitutes a bare receptor. In contrast to the light olfactory receptor, the sustentacular cells are characterized by very dense cytoplasm, containing numerous constituents of the endoplasmic reticulum and ribonucleic acid granules. The apical tip of the sustentacular cell is characterized by extensive arrangement of microvilli which project apically and interspersed between the numerous microvilli are cilia deriving from other adjacent olfactory receptors. Careful examination of serial sections of the olfactory receptors demonstrate that the cilia are approximately 0.3 to 3.0 microns in length. Since the sections that were examined routinely were on the order of 300 Angstroms in thickness, the probability of sectioning any particular cilium longitudinally, along its entire course, was highly improbable. Therefore, this information was only available from serial sections. Likewise, measurements of the length of the micro-villi, utilizing the same technique, show the micro-villi to be approximately 0.6 to 1.0 microns in length.

The central processes of the olfactory receptor cells are the unmyelinated axons which comprise the fila olfactoria. These axons

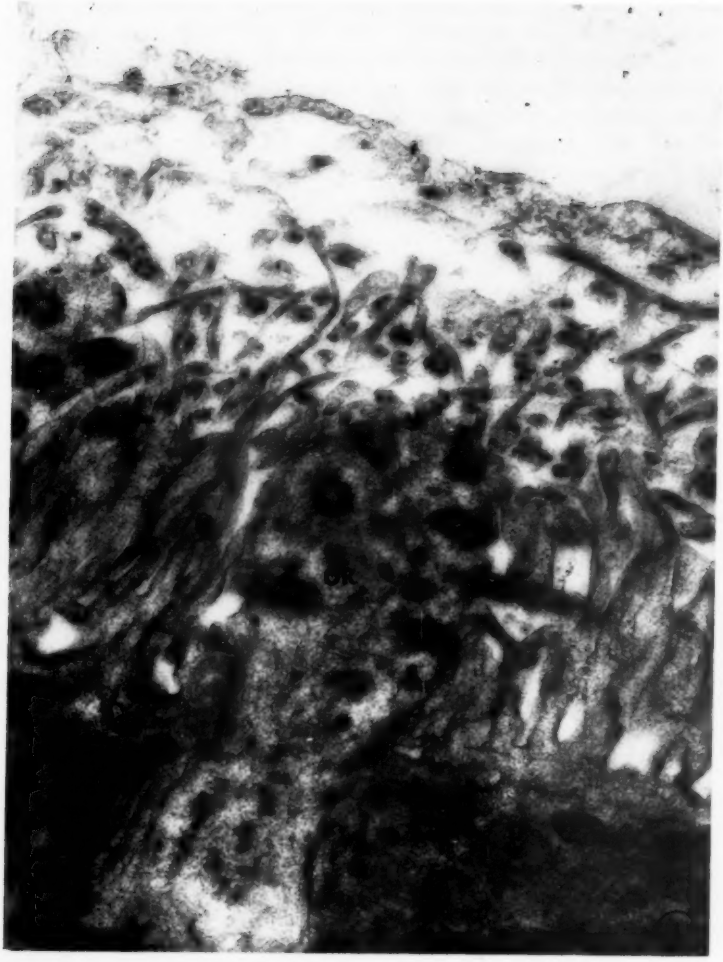

Figure 1

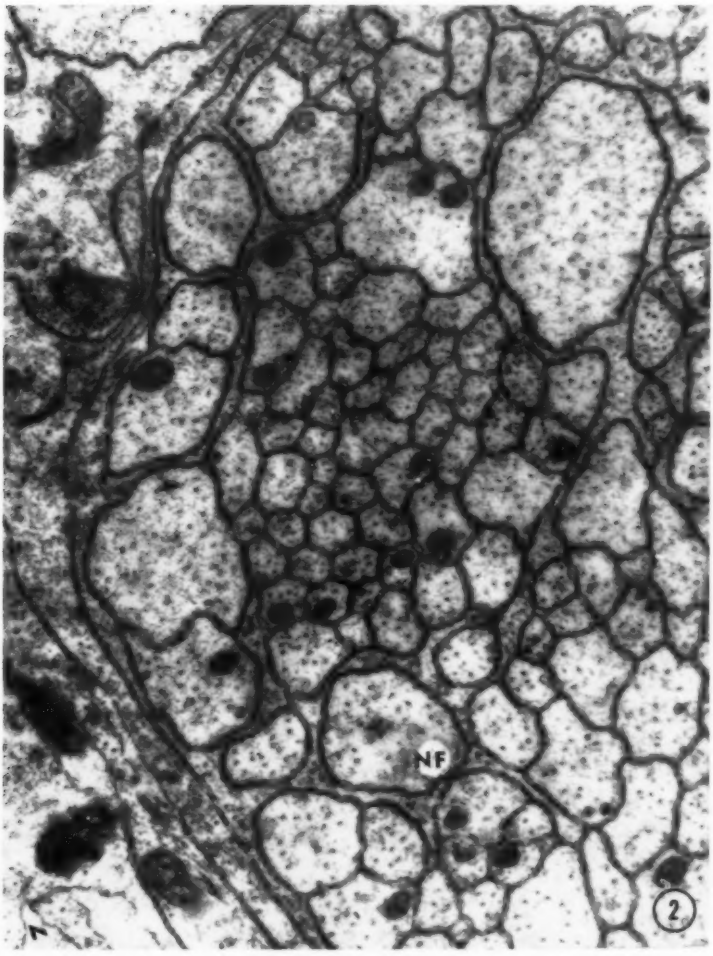

Figure 2

Figure 3

penetrate the basement membrane of the epithelium, pass through the cribrifrom plate of the ethmoid bone. They then group with others, enter the olfactory bulb and synapse in the olfactory glomerulus. As can be seen from Figure 2, the olfactory nerve fibers (NF) are extremely small in diameter. The mean diameter of these fibers is about 0.2 micron. Many of these fibers have diameters less than 0.1 micron; thus, in the light microscope these fibers would not be detected. The fine structural organization of the fila olfactoria has been more fully described elsewhere.[3,4] Figure 3 demonstrates the termination of these unmyelinated nerve fibers upon reaching the olfactory bulb. In Figure 3, to the left can be seen a large mitral cell dendrite labeled (ME). At the regions designated by the arrows, small terminal processes of the fila olfactoria are seen pushing into the dendrite in a fashion typical of synapses seen elsewhere in the nervous system.[6-9] These pre-synaptic fibers contain mitochondria and numerous synaptic vesicles. Examination of the olfactory mucus membrane throughout its extent in the rabbit has demonstrated a consistent fine structure pattern in all the olfactory receptors. Thus, in spite of their physiological heterogeniety, olfactory receptors are all identical in fine structure. Their central processes on the other hand are rather unique in that the majority of fibers are submicroscopic. The terminations of these axons in the olfactory bulb are much like synapses seen elsewhere in the nervous system.[8]

The Taste Buds. As mentioned above, since the early descriptions of the cytology of the taste buds, little attention has been paid to these most interesting structures. Much controversy still exists concerning the number of cell types and the structure of the taste pore. These problems lend themselves particularly well to an examination with the electron microscope. Figure 4 is an electron micrograph taken through the center of a taste bud of the papilla foliata of the rabbit. This figure typifies the numerous cytological differences in gustatory cells seen in any such section. Indeed, the cytological evidence suggests that many types of cells are present. Some cells, such as those labeled (A) demonstrate definite cytological characteristics of degeneration, while other cells labeled (B) are normal appearing cells containing the normal complement of cytoplasmic organelles. In view of Beider's recent observations with colchicine[2] suggesting a very rapid turnover rate in the gustatory cells, these observations are not inconsistent with physiological data. In Figure 4 one can see small pale processes containing mitochondria designated (N). These

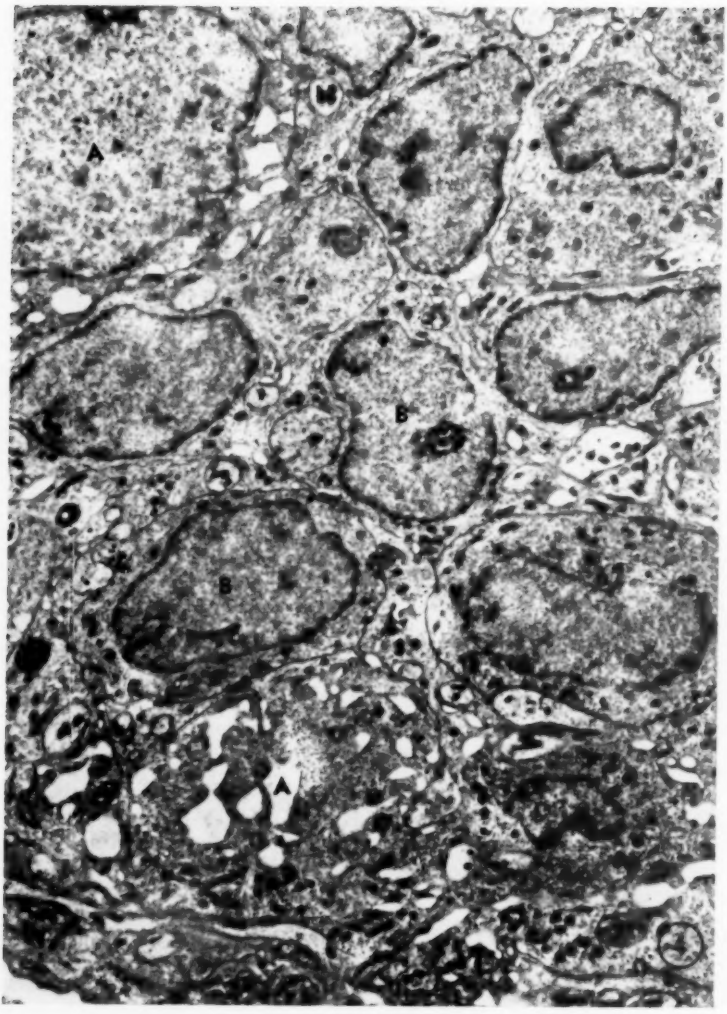

Figure 4

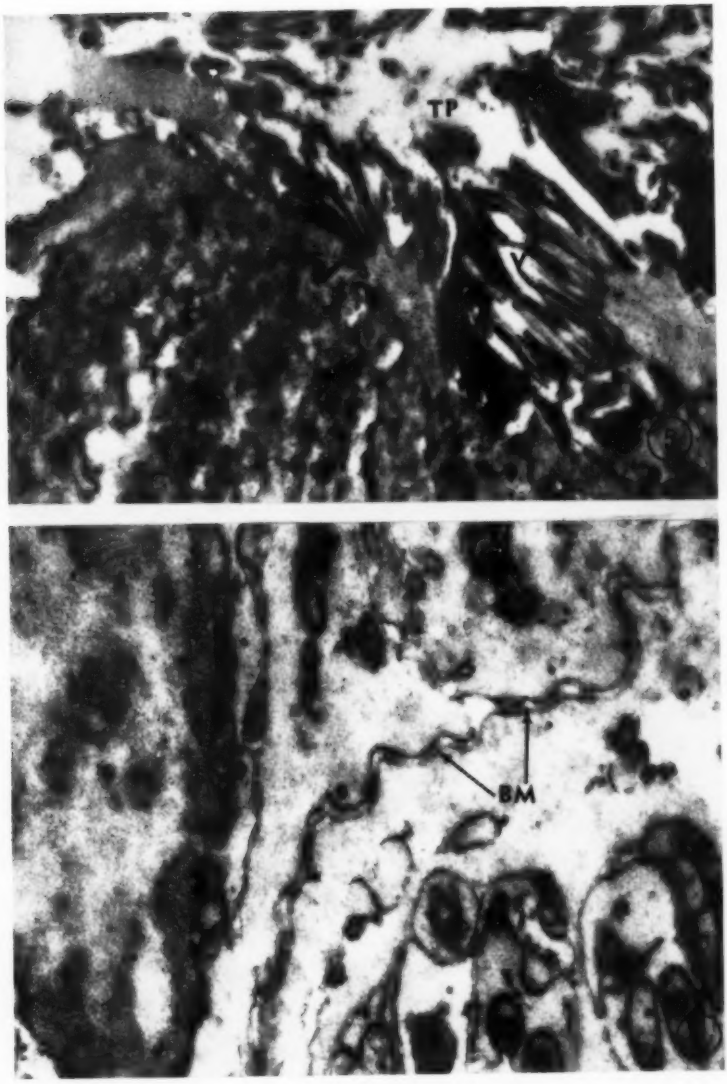

Figure 5

are the nerve fibers constituting the first order nerve cells which terminate upon the sensory receptor cell.

Of special interest is Figure 5, which is a section through the taste pore of a taste bud. To the left can be seen the non-gustatory epithelium and to the right the area of a taste pore labeled (TP). From the lower right to the upper left are located several gustatory cells. Extending from the apical tips of these cells are micro-villi (V) reminiscent of those seen in the sustentacular cell in the olfactory mucosa. Note that these processes are not hairs in any form, although gustatory hairs are traditionally described in the text books. Instead, the micro-villi are minute apical extensions of the plasma membrane of the gustatory receptor cells. Interspersed between the micro-villi is a dense osmiophilic material of unknown origin and may correspond to the "mucoid substance" of Ranvier. It is usually located between the cells as well as in the cells. Whether or not it plays a role in chemo-reception is not known. Likewise, note that there are no cilia protruding from the taste cells in contrast to the olfactory receptor cell. Finally Figure 6 demonstrates the basal portions of a taste bud. A basement membrane, (BM), designated by the arrow, separates the taste bud upper left from a nerve plexes at the lower right. The individual unmyelinated nerve fibers in the plexes constitute fibers of the glossopharyngeal nerve which will ultimately pierce the basement membrane and synapse upon the gustatory cells in the taste bud.

COMMENT

Examination of the olfactory mucosa and the papillae foliate of the rabbit with the electron microscope has made possible several interesting observations. First, in spite of the vast amount of physiological data suggesting a unique discrimination down to the molecular level in the olfactory receptor, no fine structural differences were seen in the olfactory mucus membrane of the rabbit. Secondly, examination of the taste bud of the rabbit has demonstrated a variety of cell types within the taste bud. Many of the cells appear to be undergoing degeneration and adjacent neighboring cells appear to be normal.

The gustatory cell shows, at its apical tip, an interesting structural modification, the terminal micro-villi. Cells of this type participate actively in the mechanism of pinocytosis.[5] It can be inferred,

therefore, that these cells have extremely active cell surfaces which may participate in providing extra cellular constituents with access to the intracellular environment of the cell.

Finally, it is interesting to speculate about the interactions between nerve fibers innervating the taste buds and the gustatory cell turnover rate. Since the life of an individual receptor cell seems rather brief (see Beidler, this journal), a nerve fiber must therefore reinnervate a new receptor cell upon the death of its former companion. This suggests that the nerves are at a constant state of migration and that the role of designating specificity of function is to a large extent determined by the axon to cell contiguity established at any particular time. This is a new and interesting concept; however, more evidence must be forthcoming before it can be accepted or rejected.

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XXXVII

LARYNGEAL MANIFESTATIONS OF SYSTEMIC DISEASE

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Many systemic diseases manifest themselves in the larynx. This fact should be constantly before us so we may avoid considering laryngeal disease solely as a regional problem when carrying out diagnostic and therapeutic measures.[1]

It is not intended to review all of the systemic diseases which might affect the larynx.[2-6] Discussion will center around those for which more effective diagnostic and therapeutic means are becoming available.

HYPOMETABOLIC AND HYPOTHYROID STATE

The first problem to be considered is that of the hypometabolic or hypothyroid state. In the larynx this is most often characterized by a diffuse edema, without inflammation and when biopsied, is gelatinous in character.[7] The patient may complain of hoarseness, may smoke too much, talk too much, and may have nasal infection, but a careful history will discover many systemic manifestations of a hypothyroid state and put the problem of hoarseness in its proper perspective, i.e., that of merely part of a systemic problem.

Because of the confusion and relative inaccuracy of the diagnostic tests available to determine this disease, many hypometabolic patients are denied proper replacement therapy. I feel there is a place for thyroid replacement in these borderline cases. If clear cut laboratory tests are not forthcoming I would urge therapy on clinical evidence alone, despite equivocal serum protein bound iodine levels, sedated basal metabolic rates and radioactive iodine uptake records.

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Hollender[8] has pointed out that allergic states, complicated by endocrine disturbances will be benefited by endocrine replacement. In addition, other factors such as tension, intercurrent infection and nutritional deficiencies will affect the hypometabolic state. When corrected this may allow replacement therapy or allergic therapy to be reduced or discontinued.

Hilger has stated that the hypometabolic state affects tissue healing and this in turn should be corrected before surgery is carried out.

GRANULOMATOUS LESIONS

The second problem is that of the granulomatous lesions. While we accept laryngeal tuberculosis as being secondary to pulmonary disease, we forget that the less common mycotic infections act the same way.[9] Histoplasmosis, blastomycosis and actinomycosis are rarely primary in the larynx. Search for systemic manifestations should be carried out. Specific etiological confirmation may not be available on one test such as tissue biopsy. A careful history of living, travel and working environments must be correlated with specific antigen reactions of the skin, biopsy and compliment fixation tests to arrive at a correct working diagnosis.

The granulomatous lesions of the larynx associated with chronic and recurrent diffuse infection may be part of the picture of agammaglobulinemia. Wallenborn,[10] in a recent review has emphasized the need to consider this entity and reminds us that paper electrophoresis of the serum proteins to determine the actual gamma globulin level will usually establish the diagnosis. The normal range is from 12 to 16 per cent of the total serum proteins. To measure low levels of gamma globulin, the precipitin method of measurement will detect levels not shown by electrophoresis.

Careful systemic study in the case of the noninfectious laryngeal granuloma will enable you to evaluate it so that therapy can be instituted on a more rational systemic basis.

Boeck's sarcoid is an example. This lesion may be encountered in the larynx, but is seldom primary there. Systemic search will show pulmonary lesions, as well as other diffuse systemic lesions. Cortisone therapy directed toward the systemic disease will improve and palliate both the laryngeal disease and systemic disease.

The finding of a necrotizing granuloma of the larynx, often called Wegener's granuloma is but part of a generalized systemic process of necrotizing angeitis and glomerulonephritis.[11,12] While prognosis is bad the realization that this is part of a systemic disease will stimulate more accurate observation and examination enabling further clarification and differentiation between this process and polyarteritis nodosum.

COLLAGEN DISEASE

Other systemic diseases which may be manifested in the larynx are those classified under collagen diseases.

Broadly classified they refer to rheumatoid arthritis,[13] dermatomyositis, lupus erythematosus, polyarteritis nodosum and scleroderma.

Biopsy of the larynx may reveal histologic evidence of this connective tissue disorder. When coupled with a careful history and systemic review, the systemic disease becomes apparent.

Many of these systemic diseases, with the associated laryngeal disease, are benefited by cortisone therapy. Because of this, certain aspects of such therapy should be discussed. I am indebted to Dr. William Jefferies[14] and Dr. Robert Post[15] for allowing me to draw freely from their notes and discussions relative to this aspect of the problem. The basic action of the adrenocorticosteroid is that of conversion of protein to carbohydrates, called gluconeogenesis, and control of sodium and potassium metabolism, the electrolyte regulating mechanism. A close relationship is necessary between these two actions in order to enable the body to adapt itself to changes in its environment, i.e., changes in temperature, food intake, exercise, trauma and infections. In broad clinical usage the corticosteroids are used where its anti-inflammatory effect is valuable, in auto-immune imbalance and to prevent over-response of the normal body defense reactions. The corticosteroids have been proven to be effective in the collagen diseases and many of the granulomatous diseases. Its exact mode of action is really not clearly understood. However, nearly every phase of physiologic reaction to disease or injury may be distorted. Since the inflammatory reaction may be inhibited and the antigen-antibody reaction may be prevented or reversed, these substances are of considerable benefit in diseases such as polyarteritis nodosum, rheumatoid

arthritis, sarcoidosis, lupus erythematosus, and other non-specific inflammatory or granulomatous lesions of the body. The ability to produce changes in the components of connective tissue formation, i.e., fibroblasts, collagen and ground substance, make its use especially valuable in those diseases where the pathologic physiology is primarily due to an abnormal response of the body to injury or infection. Yet, the attendant undesirable side effects of corticosteroid therapy make it necessary to use them with caution.

Retention of fluid and perforation of peptic ulcers is well known. In addition to sodium retention and potassium loss, there may be a negative calcium and nitrogen balance which in turn may have important effects on growth in children and actual skeletal demineralization in adults. This may be rapid and uncontrollable. It may result in actual muscular atrophy secondary to loss of muscle proteins from the catabolizing of the body proteins instead of building protein structures as occurs with a positive nitrogen balance.

Steroids in doses which suppress adrenocortical activities, and this may be as low as 20 mgm of Prednisone a day, may produce these and other serious changes.

A few of the more important ones other than the false sense of security provided by the anti-inflammatory action and euphoria are as follows:

A psychosis may be precipitated particularly in patients with history of emotional illness.

There may be increased blood clotting with phlebothrombosis and thrombophlebitis.

Many patients today are referred to specialists who are not aware of previous cortisone therapy being administered to their patient. Abrupt withdrawal on admission to the hospital may leave an adrenal insufficiency which may produce a shock-like state. It is interesting to note that the anesthesiologists have become quite aware of this complication and in their pre-operative rounds are checking this history carefully and ordering replacement therapy when indicated before the emergency arises in the operating room. Even slow withdrawal, after months or years of therapy, may result in a vascular

inflammatory reaction, or a polyarteritic and serositis reaction not seen before therapy.

Awareness of these complications has given us some guide to follow in our therapy.

First, we should use suppressive cortisone therapy only in cases where conventional therapy has been proven to be ineffectual.

Second, when used, it should be given in doses no larger than necessary to produce the specific action desired in the pathologic state under treatment. Small doses, i.e., 10 to 15 mgm of cortisone, may produce these effects without the undesirable side reactions of suppressive therapy.

Third, careful observation of our patients, with an awareness of the basic action of cortisone, should enable us to prevent or quickly correct any disturbance of protein or electrolyte imbalance as it arises.

Fourth, in infection problems, realizing that it takes large doses of steroids to lower resistance to infection and that the anti-inflammatory action will aid the antibiotic to reach the organism more quickly, there is every reason to consider its use here.

Lastly, we should continue to familiarize ourselves with the basic action of steroids and re-evaluate our difficult therapeutic problems in the light of this knowledge.

SUMMARY

Some of the systemic diseases which may manifest themselves in the larynx have been discussed.

An awareness of systemic disease as a factor in laryngeal disease will put proper emphasis on the need for a careful medical history and general physical examination.

Cortisone therapy is one of the more effective agents in the control of previously fatal systemic disease with laryngeal components. The basic rationale of use and the complication of steroid therapy have been discussed.

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The Scientific Papers of the American Otological Society

XXXVIII

EARLY EMBRYOLOGY OF THE AUDITORY OSSICLES AND ASSOCIATED STRUCTURES IN RELATION TO CERTAIN ANOMALIES OBSERVED CLINICALLY

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In respect to genesis, embryonic and fetal development and consequent adult form, the auditory ossicles are the most remarkable elements in the skeletal system of man. Quite as extraordinary as the way in which the ear-bones are transformed from branchial to acoustic function, is the manner in which the separate elements of the auditory apparatus originate, grow and attain maturity. Each ossicle follows a developmental course that finally leads to interdependent adulthood. Timetables here are as different from one another as the developmental

The ossicles, although derived chiefly from the branchial skeleton of the embryo, and ossified from a single center each, follow different

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A study carried out with the continuing support of the Central Bureau of Research of the American Otological Society and the National Institutes of Health of the United States Public Health Service (Grant No. B 2237).

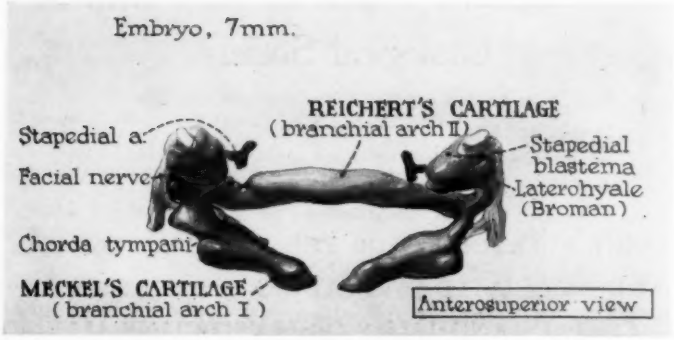


Fig. 1.—Reconstruction of the blastema of the auditory ossicles and of the branchial arches from which they are derived. Embryo of 4½ weeks (7 mm). X 32. Original reconstruction X 65.

history and adult condition of the parts when compared with corresponding features in the morphogenesis of a typical long bone.

courses of morphogenesis and at different rates of speed. The stapes of the midterm fetus has already attained adult dimensions, but is destined to undergo profound reduction in bulk before birth, after which it remains structurally quiescent. The stapes never attains the Haversian stage of typical bone; in that respect it retains lifelong fetal structure (or, rather, is already an adult bone in the fetus). The incus, on the contrary, experiences remodelling of both its periosteal and endosteal layers throughout life, yet suffers no grossly discernible loss in bulk.

All of the structural features which characterized the stapes in the late fetus and in the newborn infant are retained in virtually unaltered form in the adult: the ossicle is excessively thin; its base, like the head, is two-layered (the cartilaginous lamina of the vestibular surface investing the endochondral lamina of the tympanic aspect); mucous membrane not only covers the outer surface of the periosteal bone of the crura and head, but also coats the inner surface of the same layer where, as a result of removal of the obturator wall of the

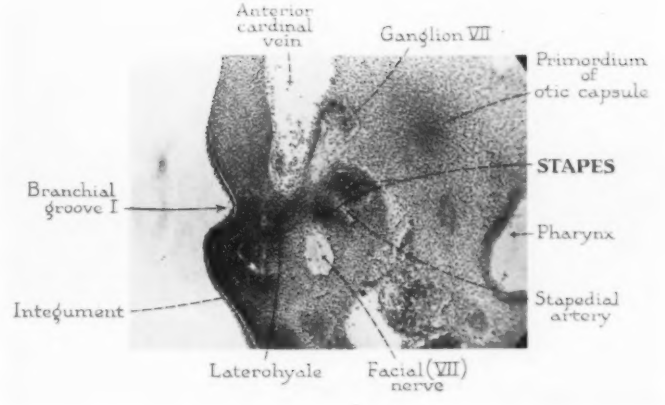


Fig. 2.—Section through the primordial tissue for the stapes near the site of contact with that of the precartilaginous otic capsule. Embryo of 5 weeks (8 mm). X 27. Original photomicrograph X 57.

ossicle, the mucosal tunic comes to replace marrow and endochondral spicules. The mucous membrane on the base of the stapes lies in contact with the endochondral lamina, which, in a process of secondary growth, formed a covering for the persistent cartilage.

The difficulties which confront the surgeon in employing one of the several techniques calculated to mobilize an ankylosed stapes are the result of the following circumstances: the anatomic position and relations of the stapes; its extreme fragility and apparent inability to heal, once it has been fractured; the power of the otic capsule to produce rapidly-growing bone in the territory of the vestibular (oval) window. All portions of the stapes are fragile; they are already frail in the infant, and will remain so throughout life. The crura and base are always thin, the head is pitted or deeply excavated, or both. The base (footplate) is usually the weakest part of the ossicle. In many cases, bone is an incomplete lamina on the tympanic aspect, *i.e.*, toward the middle ear; cartilage, persisting from the fetal stage alone then forms the base in the areas where bone is wanting.

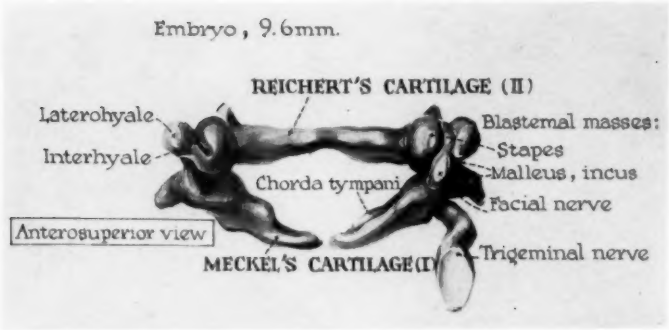


Fig. 3.—Reconstructions of the branchial structures (Meckel's cartilage and Reichert's cartilage), of the differentiating blastema of the three ossicles and the facial nerve. Embryo of 5½ weeks (9.6 mm). X 18. Original reconstruction X 65.

Earlier, the author and his colleagues reported results of their studies of the relation of the stapedial footplate to vital parts of the membranous labyrinth of the internal ear. Currently they are preparing a report on those features of normal anatomy in the middle ear which limit the "working space" in the surgery of stapedolysis, as well as those abnormal conditions in cases of otosclerosis, which act to obscure the site of pathological involvement.

Currently, interest is once more centered on those steps in early embryology which might explain aberrant growth of the ossicles (particularly of the stapes), and so provide the endaural surgeon with forewarning of possible encounter with otherwise startling anomalies.

Antecedent papers presented before this Society accounted for the developmental anatomy of the auditory ossicles, beginning with stages in which they were already formd in cartilage. As supplements to these more general discussion, three articles offered detailed information on the morphogenesis of the otic capsule,[1] the stapes[2] and the incus[3] (with atlas arrangement of figures). A fourth article, comparably concerned with the malleus, is in preparation.

However, none of these studies adequately accounted for developmental steps taken before the stage of 28 mm, in the course of

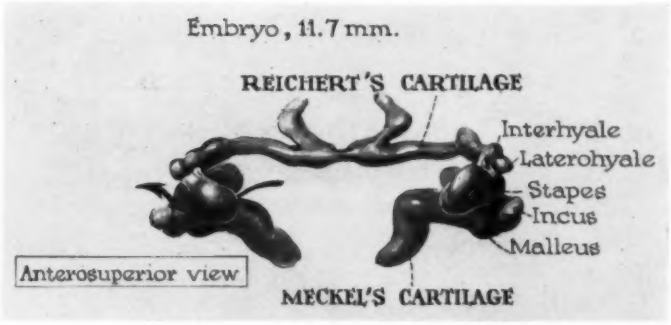
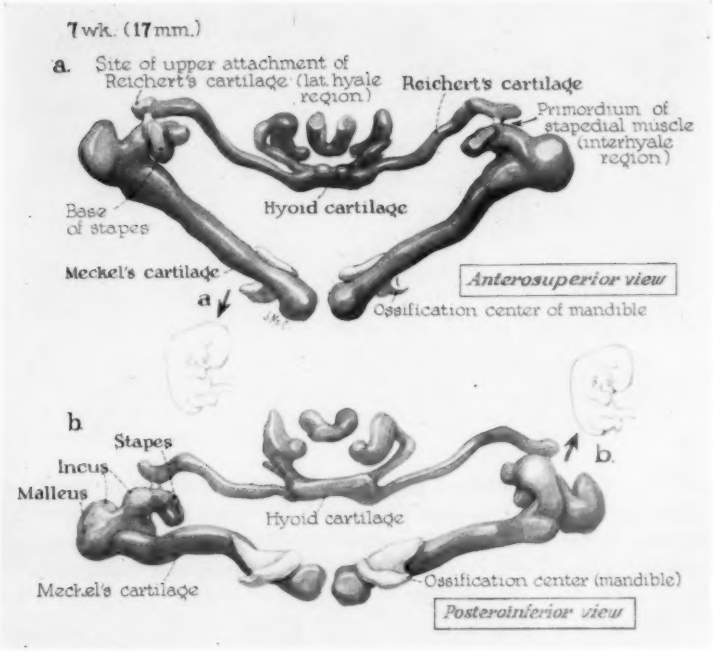


Fig. 4.—Reconstruction of the first and second branchial arches, the primitive "ossicles." Embryo of 6 weeks (11.7 mm). X 20. Original reconstruction X 60.

which progression localized portions of the mesenchyma in the branchial region suddenly became distinguishable from the tissues of which they were primordially a part and, at the same time, assume an appearance and a position predictive of their adult form and topography.

In order to determine the origin of the ossicles, it is necessary to examine them prior to the aforementioned stage, beginning with specimens in which the branchial arches and the derived "ossicles" have not yet reached precartilaginous constituency. This is the case because precocity is the governing feature of aural history: ossification begins in the anterior process of the malleus in the eighth week; in the mandible, during the seventh; in the tympanic ring, during the ninth; in the otic capsule, during the sixteenth week of intrauterine life (to be completed in a total of five weeks).

In the course of the investigation carried out by the author and his colleagues, it became apparent early that departures from the anatomic norm occurred in the ossicles, and particularly in the stapes.[1] Interest in the project was increased by the highly instructive exhibit prepared by Dr. Hough for the 1959 meeting of the Academy, which displayed photographic transparencies "representing selected views seen during the course of over 1500 routine operations for mobiliza-



Figs. 5a and 5b.—Reconstruction of the branchial and ossicular cartilages and of the ossification centers of the mandible. Embryo of 7 weeks (17 mm). X 15. Original reconstruction X 62.5.

tion of the stapes. . . ." Presented also were variations in the middle ear "where distortions of landmarks may require marked alteration in the operative procedure which the surgeon had previously planned."

Five major steps are taken in the origin and morphogenesis of the ossicles in the course of a short period of five weeks: 1) the appearance of a blastemal mass, from the primitive mesenchyma which is the source of branchial arches, auditory ossicles and other structures; 2) subdivision of the common blastema into portions predictive of the future of each; 3) the separation of the branchial arches; 4) the attainment of definite form by the ossicles and the concomitant forma-

tion of the stapedial muscle and tendon; 5) the establishment of a secondary relationship between the otic capsule and the stapes at one extremity of the ossicular group, and the proximal part of the second branchial arch at the other.

Following the account of genesis, commentary will be added on the practical application of the observations on development.

MATERIAL AND METHODS

From nine otological series we have selected five, evenly matched by intervals of one week, from the fourth to the eighth. These series are part of the collection prepared by the late Theodore H. Bast, at the University of Wisconsin, Madison, and of the collection in the Carnegie Laboratory, Baltimore, Maryland. The authors gratefully acknowledge the courtesy of Dr. James D. Ebert, Director of the Department of Embryology of the Carnegie Institution of Washington for permitting study of the valuable embryonic series in the George L. Streeter Collection (at Baltimore).

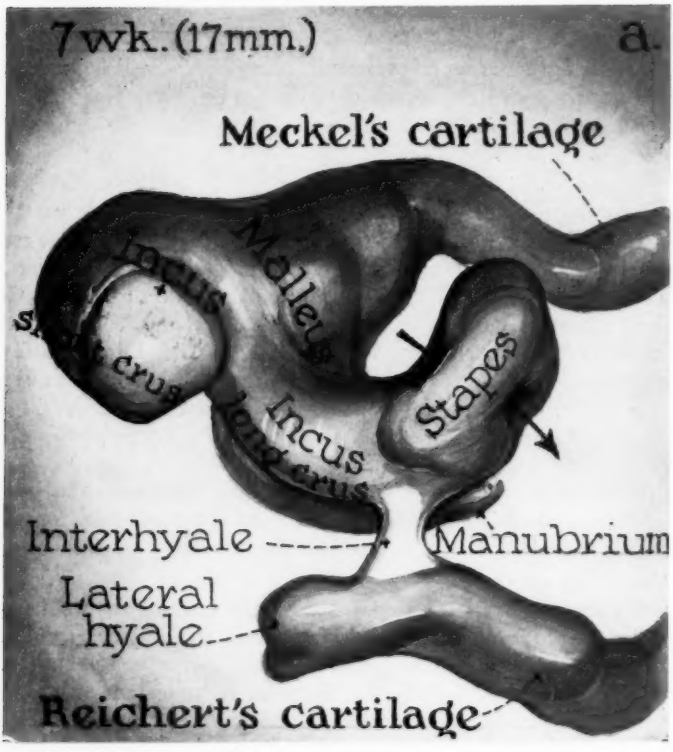
In addition to the early embryos, several more advanced specimens were studied in order to account for the fate of those parts of the branchial skeleton which are not converted into ossicles.

Reconstructions were prepared from the sections in the five otological series, to include the branchial arches, the ossicular primordia and the differentiating tissue for ligamentous and other related structures (Figs. 1, 3, 4, 5 and 7). Sections at important levels were selected as supplementary material (Figs. 2, 6b, 8, 9, 10a and 10b, 12a and 12b). Then, in order to provide a pictorial record of the several sources of the ossicles, a summarizing illustration was prepared (Fig. 11).

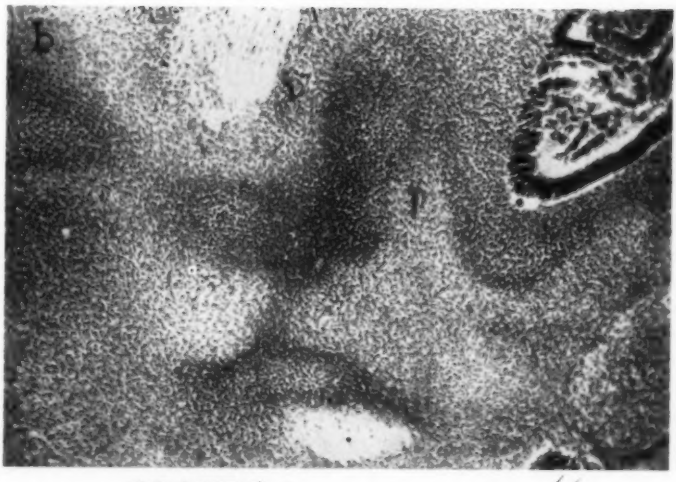
OBSERVATIONS AND COMMENT

Early Development

7-mm and 8-mm Embryos. In the embryos of approximately 4-week or 5-week stage, the precursor tissue for the auditory ossicles is a common blastemal mass, which is distinguishable from the surrounding mesenchyma only because of the greater concentration of



Figs. 6a to 6c.—Reconstruction (from cranial view), section and labelled adumbration of the latter. Same series as that illustrated in Figures 5a and 5b.



c

STAPES: base
fusion with capsule

INCUS: long crus
future articulation
with
stapes

Cochlear
duct

Cartilaginous
otic capsule

LATEROHYALE:
attachment to
otic capsule

INTERHYALE:
source of
stapedial tendon

Branchial arch II
(Reichert's cartilage)

Facial nerve

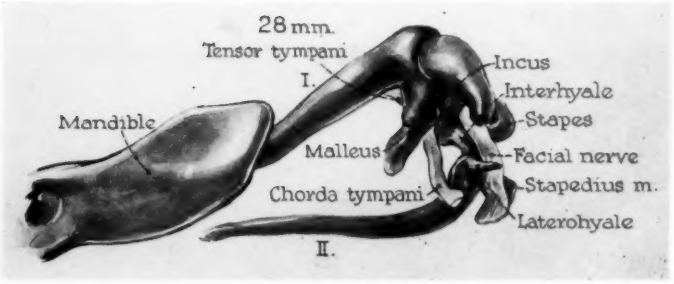


Fig. 7.—Reconstruction, seen in side-view, of the developing ossicles, the branchial cartilages, related nerves and osseous mandible. Embryo of 28 mm (8½ weeks). X 18. Original reconstruction X 62.5.

its constituent cells (Fig. 1). The primordia of the malleus and incus are not yet identifiable within this condensation of cells which will soon give rise to them.

A lobe-like portion of this mass is located at the cranial end of the second visceral bar (precursor of Reichert's cartilage), where it is grooved by the facial nerve.[5,6] Part of this mass is the primordium of the stapes. The stapedial artery extends from its source-vessel to encroach upon the anteromedial aspect of the blastema.

A mesenchymal bridge of cells between the first and second visceral bars extends from the proximal end of the mandibular bar to a point on the hyoid bar just distal to the blastemal lobe of the stapes.

The primordial stapes is already pierced by the stapedial artery, a relationship which serves to mark its obturator foramen (Fig. 1, as it does also in the 8-mm stage, shown in Figure 2).

Three other features are important, since they predict future steps in development: the entire blastemal mass is opposite the first pharyngeal groove (Fig. 2); the stapes is near the otic capsule (from

which it will derive its *lamina stapedis*); it is continuous with the laterohyale (at the site of future fusion with otic capsule).

9.6-mm Embryo. In the embryo of 5½ weeks, the enlarging blastema is divisible into two parts (on the basis of relationship with the sulcus produced by the facial nerve): one for the stapes, the other for the malleus and incus (Fig. 3).

The blastema of the stapes (its future base, or footplate) is in contact with an area of concentrated tissue which will become the fenestral part of the future otic capsule. In this zone of fusion the stapes will acquire a contribution from the capsule to form the *lamina stapedis.*

11.7-mm Embryo. Within less than a week, in the 6-week specimen, the malleus and incus have attained individual identity, through the appearance of a demarcating sulcus (Fig. 4). The stapes, already separately identifiable in an even earlier stage, is now widely perforate (Fig. 4, reader's left) and beginning to attain stapedial form through flattening on the medial aspect (adjacent to the otic capsule). The branchial arches (I and II) are now discontinuous. The area of continuity present in the preceding stage is now a remnant.

Additionally, tissue termed interhyale is now differentiating (from Reichert's cartilage) at the head of the stapes (Fig. 4, reader's right). It will give rise to the stapedius muscle and ligament. Also derived from the Reichert's cartilage (second branchial arch) is the laterohyale. This protuberance will fuse with the otic capsule in the area of the future facial canal. As this connection is about to be established, an earlier continuity is lost—that is, one between the first and second branchial arches.

17-mm Embryo. By the 7-week stage, the mandibular and hyoid bars have developed into cartilage through the greater fraction of their length, and hence may be properly termed Meckel's and Reichert's cartilages (Figs. 5 and 6a). The proximal extremity of each bar and the ossciles are still composed of precartilage; however, the malleus

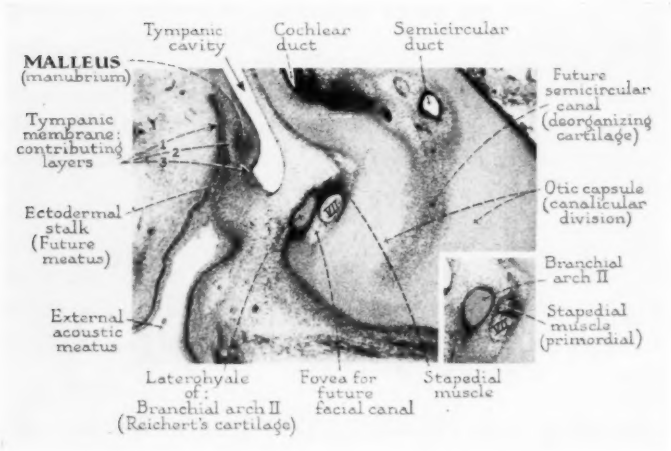


Fig. 8.—Section from the series of the 8-week fetus, at the level of the capsular attachment of the laterohyale (of the second branchial arch). Inset: section at the level of the primordial tendon of the stapedial muscle and the facial nerve (at VII). X 27. Original photomicrograph X 57.

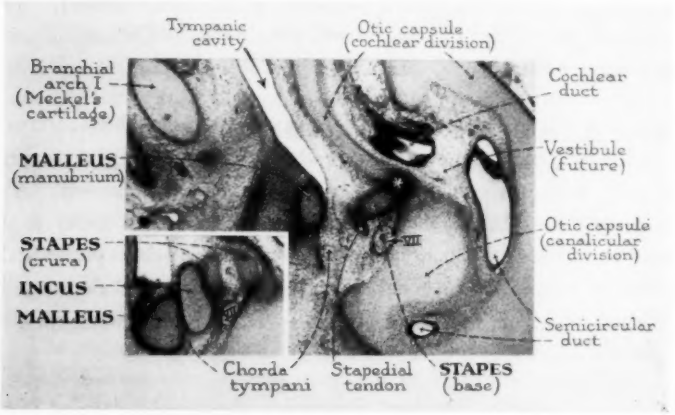


Fig. 9.—Section from the same series, at the level of impingement of the stapedial base on the otic capsule (at *). This is the site of the future vestibular (oval) window. Inset: section at the level of the stapes and stapedial artery (in the obturator foramen). X 27. Original photomicrograph X 57.

and incus are more distinctly outlined—and less a part of the mesenchyma from which they were derived.

Concurrently, ossification centers for the mandible appear as membrane bone, one on each half, formed at the distal end of the mandibular arch (Fig. 5).

In the course of their hasty preparation to subserve the function of transmitting sound, all parts of the branchial arches must undergo profound remodelling.

The malleus, now broadly continuous with Meckel's cartilage (Fig. 6a), will become detached, subsequently to be converted into a ligament.

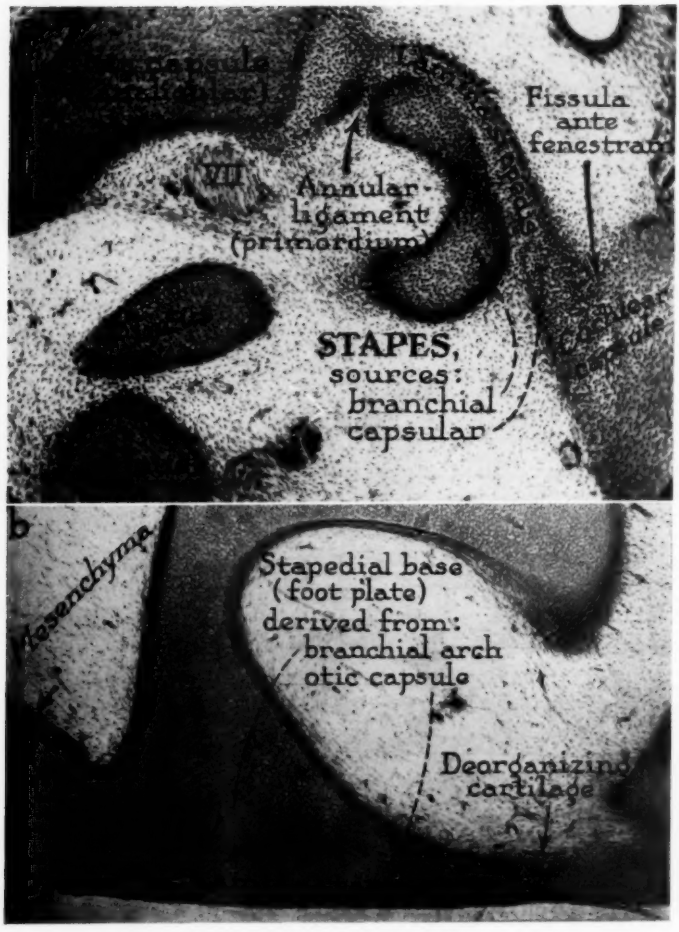
The stapes, at this stage a ring-shaped cartilage with a capacious obturator foramen (Fig. 6a, at arrow), will fuse locally with the otic caspule in the area of the future vestibular (oval) window and thereby acquire part of its footplate.

Adjacent tissue will fasten part of the second arch to the otic capsule to make part of a temporary wall of the facial canal. From similar tissue will be derived the stapedius tendon and muscle (Figs. 6b and 6c).

In no other elements of the skeletal system is reconstruction so complete as it must be to effect the changes already accomplished and which will presently occur.

Greater modifications are ahead. Small wonder, then, that the ossicles—and in particular the stapes—are subject to wide anatomic variation and to striking anomalies.

28-mm Fetus. In the 8½-week specimen the characteristic anatomical parts of each ossicle are identifiable: head, body and manubrium of the malleus (still broadly continuous with Meckel's cartilage of the second arch); body and crura of the incus; head, crura and base of the stapes (Fig. 7). Approximately 10 weeks later the anterior process of the malleus, formed early and independently in membrane bone, will attach itself to the body of the ossicle.

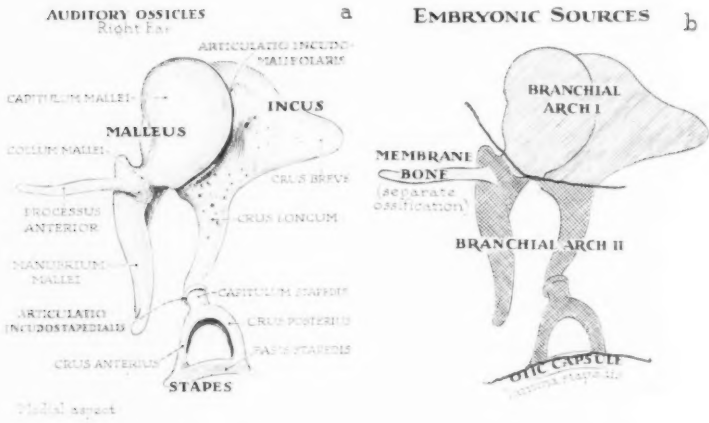


Figs. 10a and 10b.—Sections from series of the 9-week (40-mm) and 20-week (167-mm) fetuses. Demonstrating the relation (in *a* of the ring-shaped stapes to the adjacent wall of the otic capsule; and (in *b*) the line of fusion (at arrows) of the two portions and the process of deorganization of the cartilage which will separate the base of the ossicle from the fenestral rim.

This one-week period, from the 8-week to the 9-week stage (during which the embryo becomes a fetus) is a time of major importance. All elements are present in identifiable form; adult interrelationships are either established or forecast. The interhyale, continuous with the stapes, will form the tendon of the stapedial muscle; the base of the ossicle, fused with the otic capsule (in the region of the future vestibular fenestra) will receive a contribution therefrom, to its basal portion (Fig. 9, at *). Concurrently, the laterohyale has become attached to the otic capsule in such a way as to form a transitory outer boundary of the developing facial canal (Fig. 8). In the malleus, in the area of present full continuity with Meckel's cartilage, the tissue will be converted into ligament, for attachment (as the anterior ligament) to the wall of the epitympanic recess; and the anterior process, originally an independent rod of membrane bone, will become attached to the body of the malleus. By these diverse processes (transformation of constituent tissue and annexation of a once separate element) the anatomy of the malleus will be made complete.

Additionally, the endolymphatic duct-system is well formed. The perilymphatic spaces are being produced through resorption of cartilage of the otic capsule. The laterohyale (of the second branchial arch), now attached to the otic capsule, forms a temporary and partial wall for the facial canal. The facial nerve and the stapedial muscle (derived from the interhyale tissue) lie in the sulcus (the facial canal of the future) internal to the laterohyale of Arch II. Tympanic epithelium (from the pharyngeal wall) has already invested the manubrium of the malleus. This mucosal layer, together with the epidermal layer and the mesenchyma between, will form the triaminar tympanic membrane. The external acoustic meatus, which will be enlarged through opening of the ectodermal stalk, is already patent through part of its future length.

40-mm Fetus. In the 9-week fetus the cartilage of the medial segment of the ring-shaped stapes is fused with that of the otic capsule (Fig. 10). That part of the capsular wall which will contribute the vestibular lamina to the stapes is also showing peripheral zones of deorganization of the cartilage. This step in development is followed by one in which the already altered tissue will differentiate into that of the annular ligament.



Figs. 11a and 11b.—Drawings of the auditory ossicles, recording the embryonic origin of each part.

Later Development

Other changes quickly follow, ultimately to produce ossicles of multiple derivation (Fig. 11). These have been the subjects of antecedent articles.

In the fetus of 19 weeks, Meckel's cartilage is beginning to undergo ossification near the zone in which altered tissue will differentiate into that of the anterior ligament of the malleus. Three weeks later, in the fetus of 22 weeks, the anterior process of the malleus has become attached to the neck of the ossicle.

In the 24-week stage, Reichert's cartilage, continuous with the otic capsule, forms part of the wall of the facial canal. In early infancy, the cartilage (a derivative of the laterohyale) is a mere remnant. Newly-formed membrane bone and expanding tympanic cavity intervene between the contents of the canal and the residual, invested cartilage.

Passing comment is warranted, to the effect that the embryonic auditory ossicles are derived from a primitive branchial skeleton which

contributes other structures to the anatomy of the head and neck—in the case of the first arch, as far anteriorly as the midline of the mandible; in that of the second arch, to the hyoid bone. In addition to the anatomic parts of which descriptions have been hereinbefore presented, Meckel's cartilage gives rise to the stylomandibular ligament and contributes to the fetal core of the mandible; Reichert's cartilage is the source of the styloid process, stylohyoid ligament and lesser cornu of the hyoid bone.

PRACTICAL SIGNIFICANCE

It is a familiar fact that anatomic variation, important in general surgery, is a common occurrence in the bones of the skull and in many of the associated vascular, neural, muscular structures. In the present field, specific comment is warranted on variability in the styloid process (one of the derivatives of the branchial arch skeleton). This prominence varies between extremes of minute nodular excrescence to saber-like form.

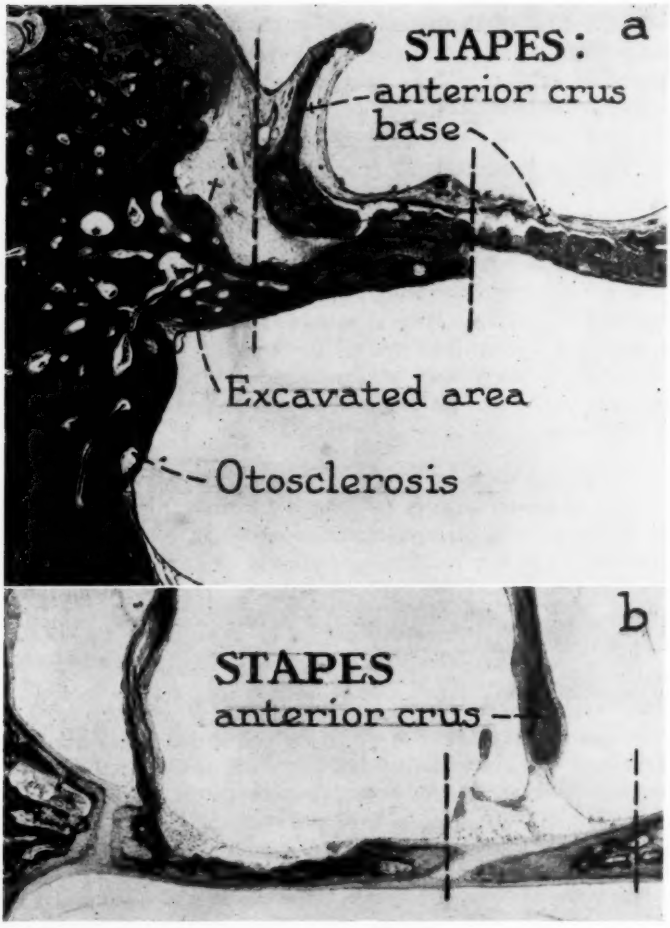
In the more specialized field of endaural surgery, it is therefore reasonable to expect equally striking departures from the anatomic norm in the ossicular derivatives of the branchial arch system. These are gradually coming to light as technical procedures permit more critical examination of the auditory ossicles. They are being sought in examination of temporal bones in laboratories from which the present article emanates.

Meanwhile the following basic observations deserve record.

Because of the manner in which the primordial stapes arises from mesenchyme of branchial position, it would be expected that some part of the precartilaginous tissue, in some specimens, would fail to differentiate, thus resulting in a partial ring. Actually, in a 14-mm embryo the result of such a failure was a stapes with a single crus.[4]

It is clear, of course, that were other portions of the annular mass of the primitive stapes wanting, both crura could be absent or the head malformed. Likewise, owing to the nature of origin of the stapedial tendon, implantation could be anomalous, or the tendon and muscle wholly absent.

Because the medial, or vestibular, part of the base of the stapes is derived from the cartilaginous otic capsule (Fig. 10), pathological



Figs. 12a and 12b.—Sections from series of adult stapes, showing the relation of the base of the ossicle to the rim of the vestibular (oval) window in a normal case (*b*) and in a case of otosclerosis (*a*).

changes that occur in the bone circumferential to the vestibular (oval) window would be expected to appear, at the same time, in the footplate. This association is known to occur, the production of otosclerotic bone being autogenetic and contemporaneous within the otic capsule and the ossicle (Fig. 12).

The progress of morphogenesis of the future ossicles is part of that which brings the entire branchial-arch system to maturity: Meckel's cartilage does not lose its continuity with malleus until the 25-week fetus; the primordial stapes is still a robust, ring-shaped segment of the branchial skeleton when, in the 9-week stage, it becomes fused with the otic capsule at the site of the future vestibular window. Together with the malleus and incus, it continues to grow as a chondral structure for an additional five-week period before ossification begins. This means, of course, that it must be profoundly altered while cartilage is giving way to bone; the ossicle has acquired stirrup shape, but the robust form suggests its origin, rather than predicts fitness for its adult function. All of the erosive changes which finally result in the fragility of the stapes are yet ahead. The processes involved are such that variation in adult configuration and weight are to be expected.

When the ring-shaped "stapes" is fusing with the wall of the vestibule, deorganization of the cartilage begins in an area peripheral to the zone of union. As the tissues blend centrally (to contribute the *lamina stapedis*), the tissue situated circumferentially is gradually converted into the precursor of the annular ligament (Fig. 10a). The form of the oval cleft which is thus produced between stapedial footplate and the fenestral rim is not uniform: anteriorly it is slanting in such a way as to cause a segment of the footplate to lie on the medial, or tympanic, aspect of the window; in other words, to override the margin (Figs. 12a and 12b).

This means, clinically, that pressure which would tend to send the stapes directly inward would find obstruction in the part nearest the cochlea. It also means that a portion of the otosclerotic bone is fully concealed, a fact of particular importance when it is realized that the area thus covered may be one in which the bone is not thickened but, on the contrary, excavated in the course of pathological involvement (Fig. 12b).

SUMMARY

A study was made of nine embryological series in the collections of the Carnegie Laboratory, Baltimore, and the University of Wisconsin, Madison. From these, five were selected for the descriptions and figures in the chief part of the present article. Supplement was made in order to account for those further steps in morphogenesis which are dependent upon the primordial form of the ossicles and of the associated structures.

Finding that three-dimensional views were requisite to full interpretation of the histological and topographical changes observed first in the sectioned material, reconstructions of seven of the nine stages were prepared.

Development is traced through the following stages: 7 mm; 9.6 mm; 11.7 mm; 17 mm; 28 mm; 40 mm. The advancements rapidly made during a brief four-week period (from 4½ to 8½ weeks) are those which, in constituting the story of development from the appearance of ossicular blastema to the assumption of typical form by the three ear-bones, provide a basis for interpretation of anomalies and an introduction to the succession of stages which bring the ossicles to maturity.

Commentary is added to apply the observations to a solution of some of the problems which confront the surgeon in operations on the stapes.

303 East Chicago Ave.

The drawings were executed by Miss Jean McConnell. The photomicrographs were taken by Mr. Homer Montague and were labelled by Miss Rosamond Howland.

The illustrations were prepared from the following series in the G. L. Streeter Collection, Carnegie Laboratory, Baltimore: 617 (7 mm); 6517 (9.6 mm); 6524 (11.7 mm); and from the T. H. Bast Collection, University of Wisconsin: 10 (17 mm); 158 (28 mm); 168 (40 mm).

Figures 1, 3, 4, 5 and 7 from Hanson and Anson, 1959, are reproduced with the permission of the Quarterly Bulletin of Northwestern University Medical School.

Translations of the German literature prepared by Mrs. Eycke Strickland have been used to guide the course of the present study. A complete presentation of the literature on early embryology of the ossicles by Mrs. Strickland and the present authors is in preparation.

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XXXIX

COMPONENTS OF ELECTRICAL RESPONSES RECORDED FROM THE COCHLEA

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Electrical responses of the cochlea to acoustic stimuli are, in general, complex mixtures of several components. These components have been designated: 1) cochlear microphonic potential (CM), 2) action potential (AP), and 3) summating potential (SP). The N_1 of the action potential (AP) represents the synchronous firing of the auditory nerve fibers, while CM and SP represent end-organ activity. More detailed descriptions of certain properties of these components have been given by Davis.[2,3]

In order to study these components systematically, it is desirable to separate them. One method of obtaining CM without contamination by AP is by recording responses from totally denervated cochleas.[13] It is well established that cutting or crushing the auditory nerve, without damaging the blood supply to the cochlea, results in degeneration of the spiral ganglion cells, but leaves the organ of Corti intact.* [7,9,15] However, the electrical responses from denervated cochleas have not been extensively studied. The present paper con-

* This is not the place to consider the possible effects that the sectioning and possible regeneration of efferent fibers may have upon CM and SP.

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This work was supported in part by the U.S. Army (Signal Corps), the U.S. Air Force (Office of Scientific, Air Research and Development Command), the U.S. Navy (Office of Naval Research), and research grant B-1344, National Institute of Neurological Diseases and Blindness of the National Institutes of Health, Public Health Service.

cerns responses from such cochleas with particular emphasis upon the separation of the component potentials.

Six cats were prepared with denervated left cochleas and intact right cochleas. One to five months after the nerve had been sectioned, each cat was anesthetized (Dial, 75 mg/kg) and responses from both cochleas recorded with electrodes located on the bone near the round window.

Responses from the Normal Cochleas. Figure 1 shows a response to a click 50 db above visual detection level (VDL). This intensity permits us to identify separately CM and AP(N_1). At low intensities CM reverses completely when the polarity of the click is reversed, whereas AP shows little change. This circumstance makes it possible to average equal numbers of responses to rarefaction and condensation clicks to cancel CM and obtain AP alone. (The prominence of the CM component can also be minimized by averaging a large number of responses to short bursts of noise. Details of these techniques are given in reference 1.)

SP is easily distinguished from CM and AP if we stimulate with "long" bursts of high frequency tones or noise. SP is then seen as a shift in baseline which persists throughout the duration of the bursts.

CM, AP, and SP from Denervated Cochleas. A click response recorded from a denervated cochlea does not show the AP component of Figure 1. If the amplitude of the CM component is plotted for different click repetition rates, one obtains the curve shown in Figure 2. It is easily seen that the amplitude of CM is unaffected by the rate of stimulation as long as responses to successive clicks do not overlap. The flatness of the rate function for CM is consistent with observations that CM has no refractory period and shows no effects of fatigue or adaptation for moderate intensities of stimulation.[2]

If a rate function is plotted for AP of a normal cochlea, one obtains the curves similar to those traced by x's in Figure 3. In this experiment bursts of noise were used as stimuli and the responses averaged so as to obtain AP alone. Rate functions for noise bursts and clicks of comparable intensities and duration are almost identical. The point to be emphasized is that the amplitude of AP decreases rapidly with stimulus rate for rates above 10/sec. Comparison with Figure 2 shows clearly that CM and AP behave quite differently with

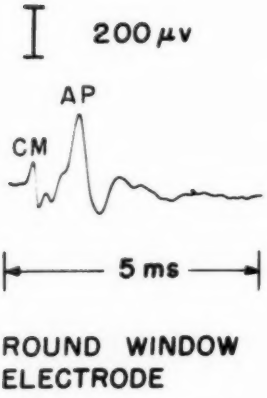

Fig. 1.—Cochlear response to a click recorded with a round window electrode. In this and subsequent figures, upward deflection indicates negativity at the round window with respect to the headholder (reference electrode); CM labels most prominent and earliest part of the cochlear microphonic potential; AP labels the N_1 component of the action potential of the auditory nerve.

changes in stimulus repetition rate. The curve formed by the dots in Figure 3 represents the rate function for a small potential found in the responses of one "denervated" cochlea. (Note especially that the amplitudes for the curves are normalized and that the ordinate values are given as per cent of the relevant maximum amplitude.) In terms of absolute voltage, the potential for the denervated (left) ear is less than 1 per cent of that for the right ear, and would virtually be undetectable by visual inspection, i.e. without the use of averaging techniques. The striking similarity of the normalized rate functions for both ears leaves little doubt that the small potential found in this denervated ear is a residual AP resulting from incomplete section of the auditory nerve. Histology confirmed that a significant number of spiral ganglion cells had indeed been spared. The rate function is thus apparently a valuable criterion in identifying neural components of cochlear responses.

Figure 4 shows responses recorded from both a normal and a denervated cochlea to a 10 millisecond tone burst of relatively high intensity. AP is clearly seen in the response of the normal cochlea,

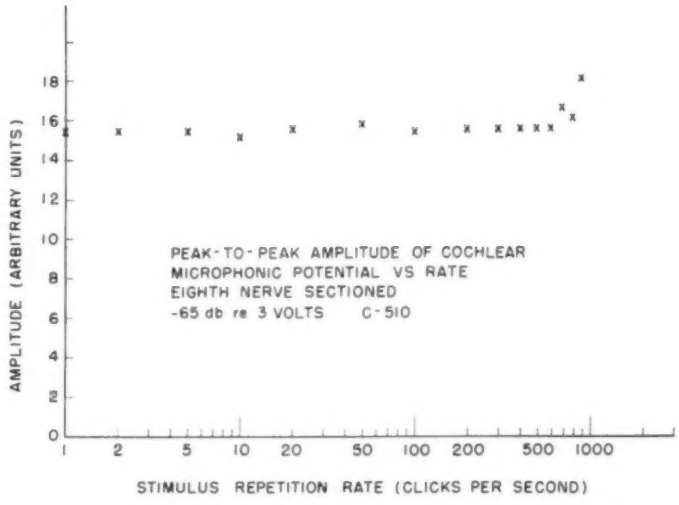

Fig. 2.—Graph showing the amplitude of CM as a function of stimulus repetition rate. Amplitude of CM is approximately 50 μ volts. Amplitude rate curves will be referred to as rate functions.

while CM is indicated by the thickening of the trace for the duration of the burst. SP is represented by the downward deflection of the baseline (middle of thickened trace) during the presence of CM. AP cannot be seen in responses from the denervated cochlea, but no great differences between the two ears are observable in SP or CM.

The "Slow" Potential. As Davis has shown, the summating potential (SP) is prominent only at high stimulus intensities.[4] CM can be cancelled by averaging responses to low intensity condensation and rarefaction clicks. AP can be eliminated by denervation. Accordingly, no response component should be observable when responses to low intensity condensation and rarefaction clicks from denervated cochleas are averaged. This, however, is not the case. Figure 5 shows the results as a function of click intensity. There is a slow negative potential which grows with increasing intensity from −100 db to about −60 db. This potential is present in responses to either click polarity and can therefore not be CM. In Figure 6 the

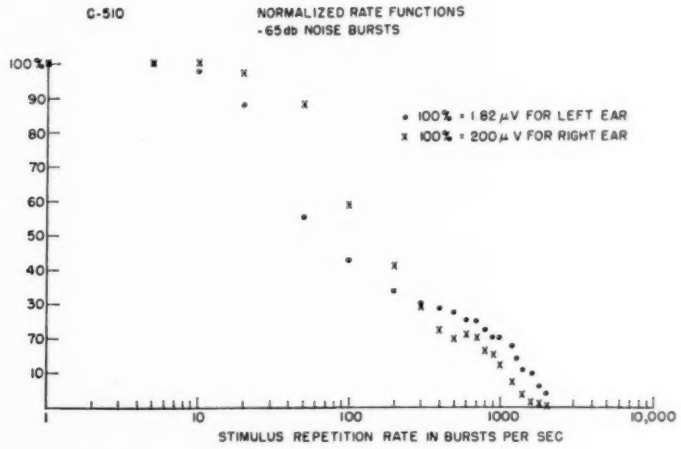

Fig. 3.—The rate function for AP from a "denervated" left cochlea is compared with the rate function for the normal right cochlea in the same animal. The response amplitudes have been normalized to make comparisons of the two curves easier. Stimuli were bursts of noise (duration: 100 msec; intensity: −65 db re 1.0 v rms).

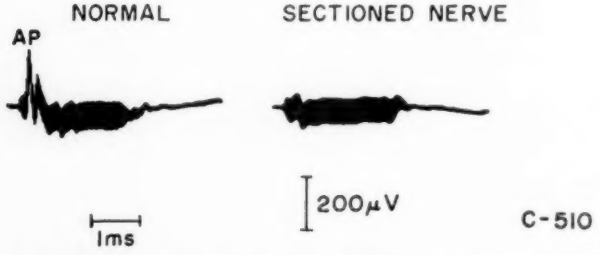

Fig. 4.—Responses from a normal and denervated cochlea in the same cat to a 7 KC tone burst (10 msec duration; 1.0 msec rise and fall time. Intensity: −20 db re 1.0 V rms).

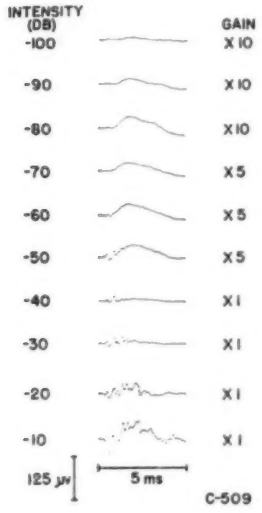

Fig. 5.—The traces shown are obtained when equal numbers of responses to condensation and rarefaction clicks are averaged for different stimulus intensities (denervated cochlea). Reference level of clicks: 3.8 Volts into PDR-10 earphone. Gain changes were necessary to obtain responses of comparable size. The calibration marks refer to the traces of lowest gain. At higher stimulus intensities the "fast" deflections correspond to imperfectly cancelled CM (non-linear part).

growth of this slow potential with intensity is contrasted with that of CM for the same cochlea. This intensity function for the slow potential does not correspond to functions given by Davis for the negative summating potential.* [4] However, it is possible that this

* A note must be interjected regarding conventions with respect to electrical signs. Potentials recorded by electrodes placed in scala vestibuli or scala tympani provide the basis for the designation of positive and negative summating potentials.[12] An electrode placed near the round window and referred to neck or headholder is polarity equivalent to an electrode placed in scala tympani with the same reference electrode. For potentials which reverse polarity as one passes from scala tympani to scala media, the nominal polarities for these two electrode systems will be reversed. This is the case for the CM and SP, but not for the AP. Davis' negative summating potential would therefore be nominally positive for our electrode arrangement. We do not know at present whether our "slow potential" reverses in polarity between scala tympani and media.

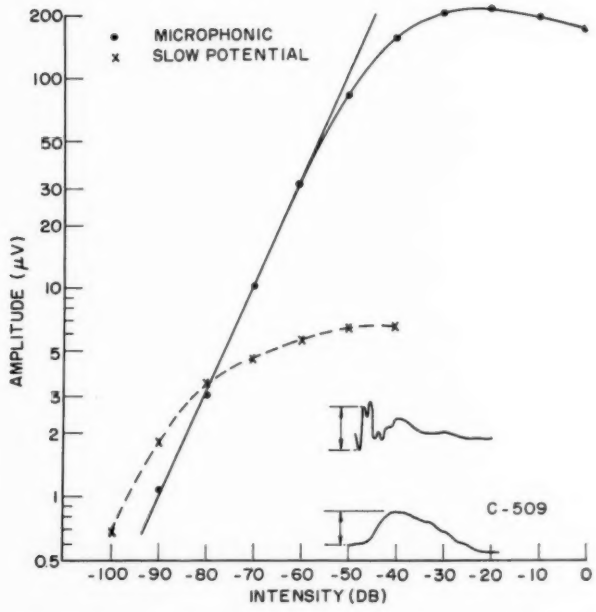

Fig. 6.—Intensity functions of the "slow potential" and CM from the same denervated cochlea. The CM was obtained by measuring responses to rarefaction clicks. The "slow potential" curve was plotted using the data of Figure 5. The insets on the right show the criteria used in measuring CM and slow potential respectively. Reference level of clicks: 3.8 volts.

slow potential may correspond to what Davis calls the positive summating potential, which apparently can be seen at lower intensities than the negative summating potential.[3]

What is the evidence that the slow potential is not AP? Figure 7 shows the slow potential as a function of click rate: it is unaffected by stimulus repetition rate until the individual responses overlap, whereas we have seen that AP from normal, and even partially denervated, cochleas decreases sharply in amplitude at rates above 10/sec (Fig. 3). Responses to long bursts of noise provide further evidence that the slow potential is not AP (Fig. 8). The slow potential lasts

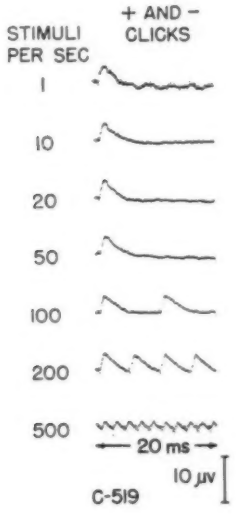

Fig. 7.—Responses from a denervated cochlea showing the "slow potential" as a function of click repetition rate. Responses to condensation and rarefaction clicks were averaged to cancel CM. Intensity: −60 db re 4.0 volts.

as long as the bursts of noise that stimulate the ear. In this respect, the slow potential resembles SP. For a nominal onset latency of CM of 0.3 msec, the onset latency of the slow potential is about 0.7 msec, while the onset latency of AP for a normal cochlea under comparable conditions is about 1.0 msec. Since Pestalozza and Davis[12] report that the onset latency of SP is indistinguishable from that of CM, these data are further evidence that the slow potential is neither CM, SP, nor AP.

A slow potential can also be detected in the responses of normal cochleas. Under appropriate stimulus conditions such as long bursts of noise at intensities near the threshold of AP (VDL), a slow potential is seen whose duration is related to burst length.

There are strong reasons for believing that the slow potential discussed in this paper plays an important role in the initiation of

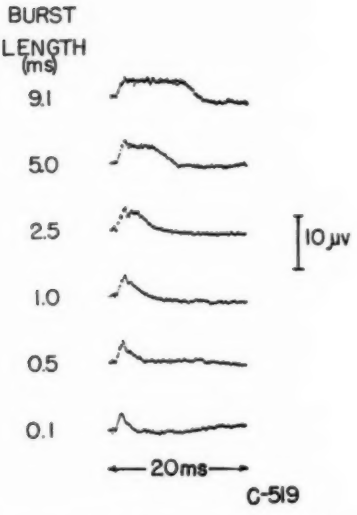

Fig. 8.—The "slow potential" in response to burst of noise of different duration. The traces were obtained by averaging 256 successive responses; thus CM is effectively minimized. Intensity of noise bursts: −60 db re 1.0 volts. The beginning of each trace is synchronized with the onsets of the bursts.

nerve impulses at low sound intensities.[11] The existence of a potential other than CM which may initiate auditory nerve impulses at low intensities fits in with some otherwise puzzling observations according to which a good-sized AP can still be observed, while CM is small or undetectable. Such observations are frequently made under conditions of low intensity sound stimulation, acute damage to the cochlea,[5] or cochlear poisoning by antibiotics.[4,8] These findings, the evidence presented here and in another forthcoming paper[11] all lend credence to the view that the initiation of auditory nerve impulses may depend on several mechanisms. Since these mechanisms function apparently in different intensity ranges, they enable the auditory system to cover the enormous dynamic range over which it actually functions. Throughout the years, workers have speculated and presented evidence regarding the role that the external and internal hair cells play in the transduction of acoustic stimulation into electrical impulses.[10,14]

More recently, physiological data have been presented that make the existence of several mechanisms (or of several neural populations) plausible.[4,6] The present paper contains data that strongly support a pluralistic approach to the study of what are now called mechanisms of sensory coding.

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Acknowledgments. We wish to acknowledge the participation of Dr. M. H. Goldstein, Jr., in some of the experiments reported here, the help of Mr. R. M. Brown in matters of instrumention, the assistance of Miss P. E. Palmer in surgical procedures, and of Mrs. A. S. Maccoby in histology. The assistance of Professor W. A. Rosenblith during the course of experimentation and in the writing of the manuscript is also gratefully acknowledged.

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XL

HUMAN COCHLEA RESPONSES TO SOUND STIMULI

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The first cochlear potentials were recorded from cats by Wever and Bray in 1930.[8] Since then cochlear potentials have been recorded in a number of other species. There has been difficulty in recording the potentials in man. In 1935 Fromm, Nylen, and Zotterman[3] tried to record cochlear potentials from man using headphones to evaluate their intensity. They observed a small response in two out of ten cases. Andreev, Arapova, and Gersuni[1] in 1939 reported studies of twenty subjects using a cathode ray oscilloscope to measure their potentials. Their records showed small potentials except in one instance when a 20 microvolt response to a tone of 200 cycles per second was recorded. The report stated that sound stimuli of such intensity were used that they were painful to the ears of the observers. In 1941 Perlman and Case[6] published the first picture of the human cochlear potential. This potential was obtained by placing an electrode against the round window through a perforation in the tympanic membrane of an unanesthetized patient. The resulting response was small and just above the noise level of their amplifiers. Lempert, Wever, Lawrence, and Meltzer reported in 1947 and again in 1950[4,5] that in about one half of their cases they were able to achieve a cochlear potential of one microvolt.

In 1959 observations in four individuals were reported from the Neurophysiology Laboratory of the Department of Otolaryngology

Supported by grants in aid from the National Institute of Neurological Diseases and Blindness and the Alfred Sloan Foundation.

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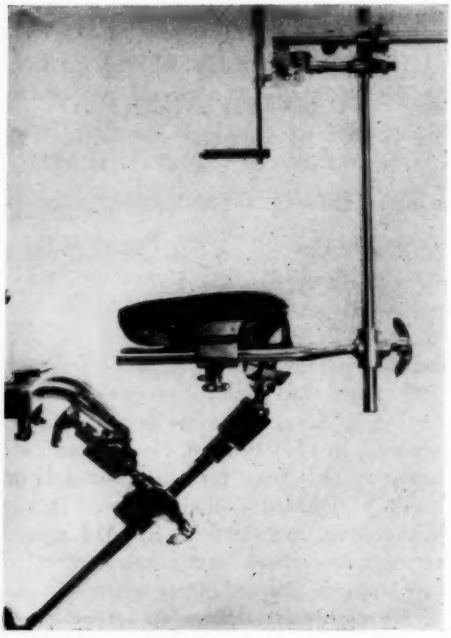

Fig. 1.—The micromanipulator mounted on the head rest.

at the Johns Hopkins Hospital.[7] Two of these developed cochlear potentials in excess of ten microvolts. Thirteen more cases have been investigated and twelve of this group are to be reported today. The most recent case will be mentioned, but as it was done in the last four days, there was insufficient time for complete record analysis.

METHOD

In order to record the cochlear potential from the round window in a routine fashion in human subjects, it was found to be necessary to build a stable electrode holder (Fig. 1). This consists of an upright attached to the head holder of the operating table and a side arm extending over the head of the patient. Three micromanipulators are

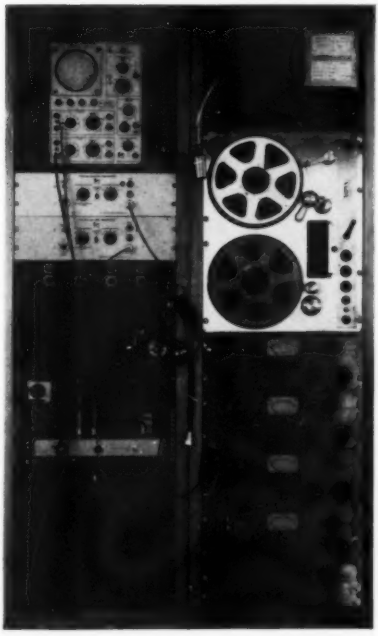

Fig. 2.—The portable stimulating and recording console as used in the operating room.

mounted on this arm in such a fashion as to enable the surgeon to place the electrode accurately on the round window membrane. The whole assembly is built to allow for sterilization. Electrode placement is done using a Zeiss operating microscope.

The electrodes are fabricated from No. 28 platinum wire tipped with a ball or No. 28 silver wire with a flattened end. They are insulated with teflon tubing and can be autoclaved.

The stimulating and recording equipment, built into a console activated by a foot switch, consists of a four channel Ampex type 300-4 tape recorder with a series of preamplifiers. A series of pure

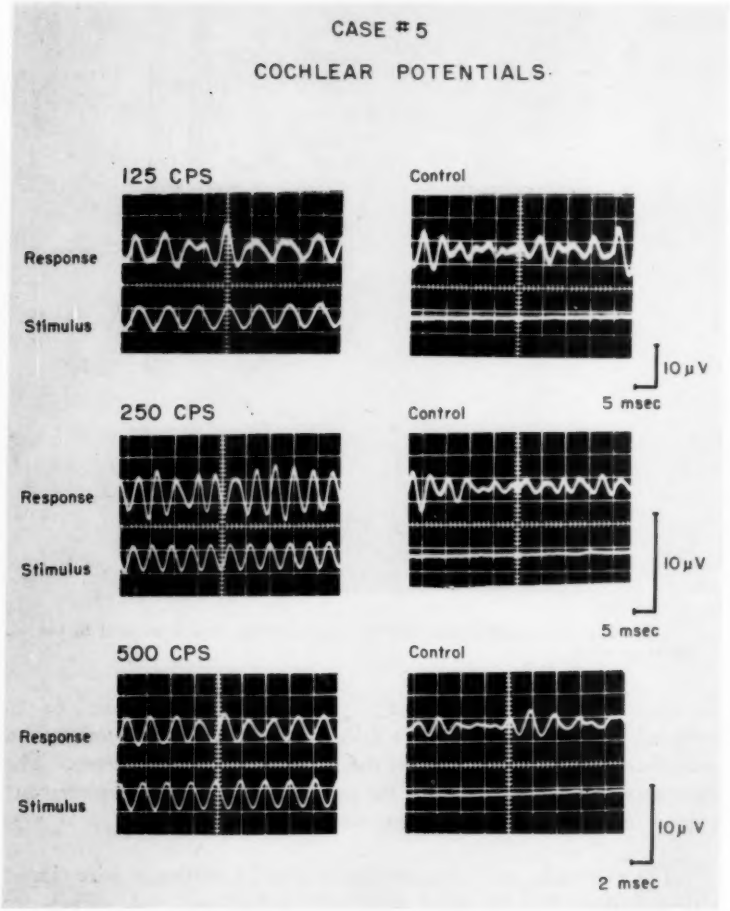

Fig. 3.—Case 5 (otosclerosis). Cochlear potentials obtained for 125, 250, and 500 cycles per second.

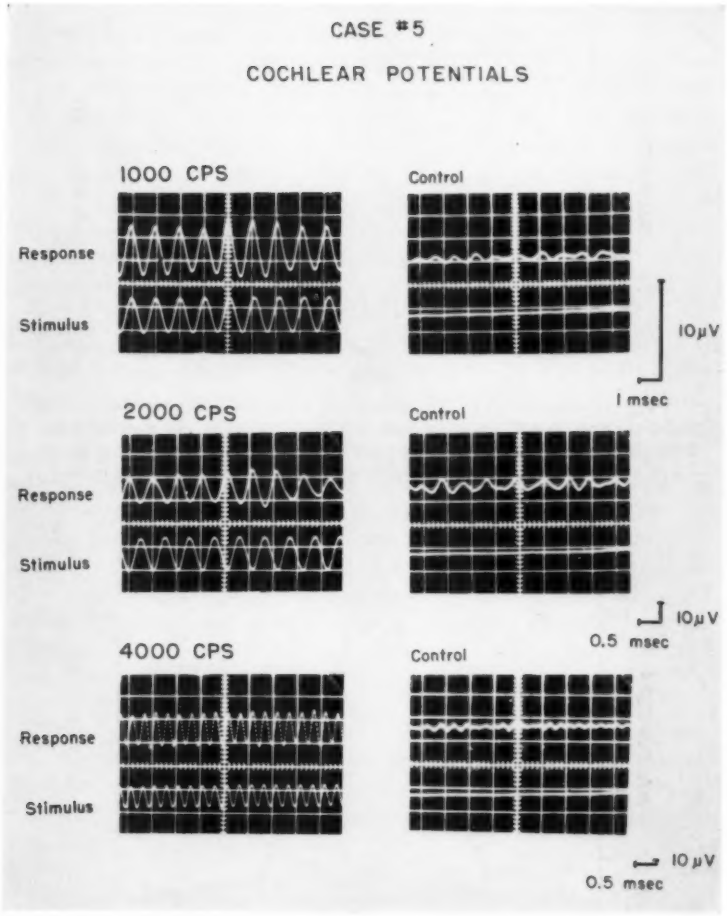

Fig. 4.—Case 5 (otosclerosis). Cochlear potential obtained for 1,000, 2,000, and 4,000 cycles per second. The response at 4,000 cycles per second is 63 microvolts, the largest cochlear potential recorded.

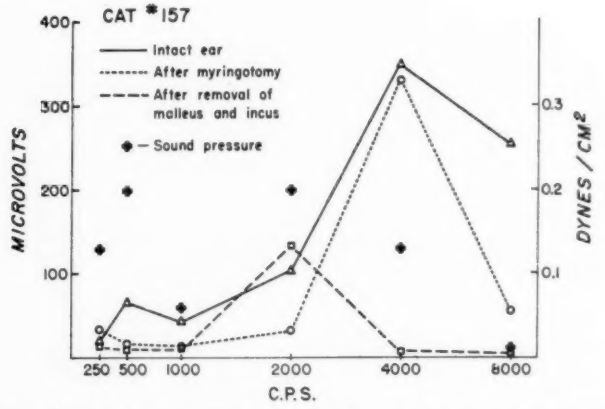

Fig. 5.—Cat No. 157. The animal was stimulated using the patient tape under the same conditions as the human. The cross shows the sound pressure level. The animal is seen to have a profound drop in all frequencies except 2,000 cycles per second after interference with the conduction apparatus.*

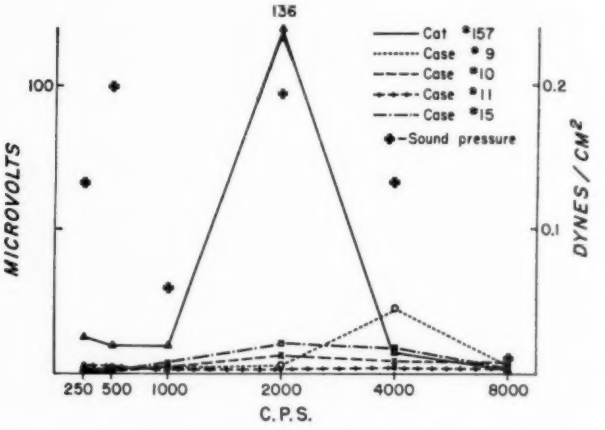

Fig. 6.—The cochlear potential of cat No. 157 after myringotomy and disarticulation of the crura of the stapes plotted on the same scale as four cases. The sound intensities were the same for the human as for the cat. Note the similarity in cochlear potential between the species in the higher frequencies.*

* Erratum. Scale of dynes per cm² (Figs. 5, 6) to read x 20, i.e. 2,4, and 6 dynes per cm².

tones of different intensities and clicks are recorded on a tape. This is then recorded on a second tape with constant settings. The second tape then is a matrix tape and the first a master tape. From the matrix tape a number of patient tapes, which are used to stimulate the patient, are made using the same constant settings. Thus a series of patients are given identical stimuli. The patient tape is played through an audio-amplifier which is adjusted to reduce the overall noise at a little above human threshold. The audio-amplifier activates a speaker. The stimuli are delivered to the patient through a four foot, flexible brass tube with a teflon tip. The tip is placed about two and one half centimeters from the external canal of the ear. The tube and tip may be sterilized.

The output of the patient tape played through the speaker, flexible tube and tip, is calibrated at a distance of two and one half centimeters from the proximal end of the ear speculum used in the operative exposure of the round window. One centimeter from the distal end of the speculum a Western Electric No. 640 AA condenser microphone is mounted. The corrected reading from the microphone is then converted to sound pressures measured in dynes/cm^2.

The first stage of amplification is a Tektronix type 122 low level amplifier which has been set to record from 8 cycles per second to 20,000 cycles per second. The output of the amplifier is led into a Tektronix type 502 cathode ray oscilloscope and the response is viewed on the screen as the output of the cathode ray oscilloscope is recorded on the tape.

The input to the third channel of the tape recorder is a microphone which monitors the comments during the operation. A foot switch near the surgeon's chair activates the console simultaneously to stimulate the ear and record the round window response and the verbal comments of the surgeon.

The patient is grounded with a large cautery ground under the buttocks. The shield of the pick-up electrode cable is grounded to the speculum. The responses are recorded with respect to an indifferent electrode in the temporalis muscle.

The equipment was carefully tested to determine if there was any significant distortion or if there were artifacts in either the recording or playback systems. Numerous experiments were made with cats.

CASE 11

COCHLEAR POTENTIALS BEFORE MOBILIZATION

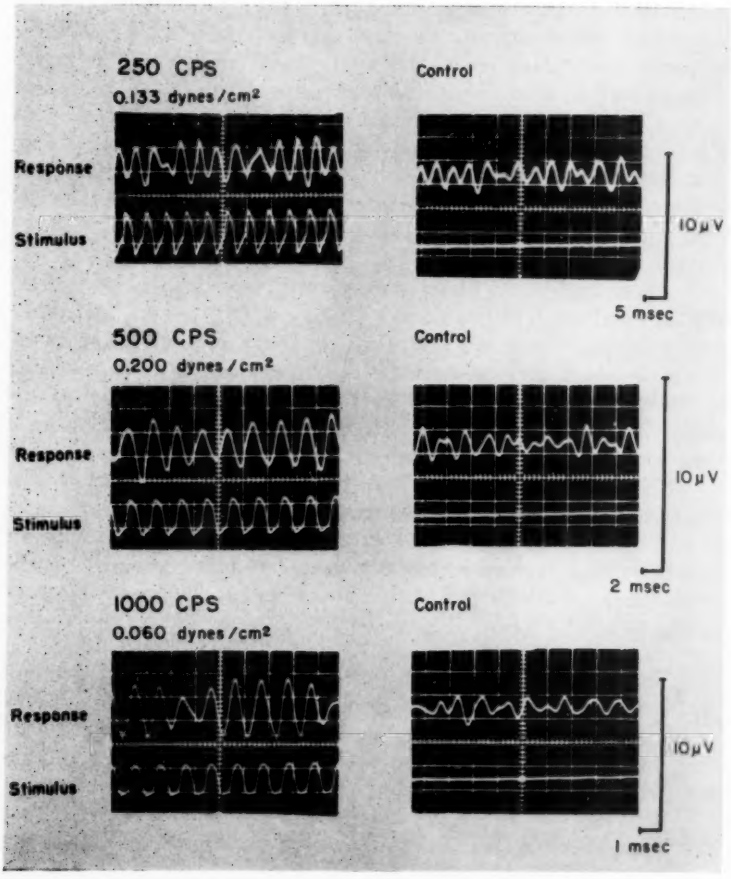

Fig. 7.—Case 11 (tympano-mastoiditis). Cochlear potentials obtained for 250, 500, and 1,000 cycles per second before mobilization of the stapes from scar tissue.**

** Erratum. Calibration Figures 7, 8, 9, and 10 for sound pressure should be

250 cps - 3 dynes/cm²	1000 cps - 5 dynes/cm²	4000 cps - 3 dynes/cm²
500 cps - 4 dynes/cm²	2000 cps - 5 dynes/cm²	8000 cps - 1 dyne/cm²

CASE 11

COCHLEAR POTENTIALS BEFORE MOBILIZATION

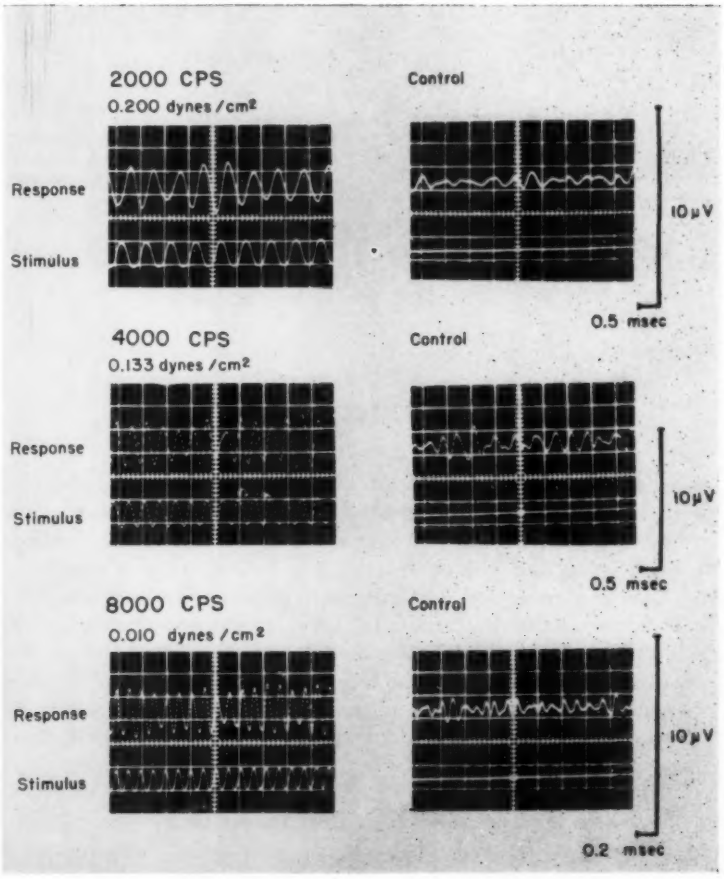

Fig. 8.—Case 11 (tympano-mastoiditis). Cochlear potentials obtained for 2,000, 4,000, and 8,000 cycles per second before mobilization of stapes from scar tissue.**

TABLE I

SUMMARY OF RESULTS OF 17 PATIENTS ON WHOM ATTEMPTS WERE MADE TO RECORD COCHLEAR POTENTIALS

		STIMULI EMPLOYED					
		LOW TONES 125 - 1000 CPS		HIGH TONES 2000 - 8000 CPS		CLICKS	
TYPE	NUMBER OF PATIENTS	RECORDING ATTEMPTED	POSITIVE RESPONSE	RECORDING ATTEMPTED	POSITIVE RESPONSE	RECORDING ATTEMPTED	POSITIVE RESPONSE
Tympano-mastoiditis	11	11	6	11	7	6	1
Otosclerosis	5	5	4	5	5	5	4
Congenital neurosensory deafness	1	1	0	1	1	1	0
TOTAL	17	17	10	17	13	12	5

Photographs of the face of the cathode ray oscilloscope tube and tape recordings were made simultaneously of the round window response to tones and clicks. The tape was then played through the cathode ray oscilloscope and photographed. The two series of photographs were then compared and no detectable difference was seen in either the cochlear potentials or the VIII nerve action potentials. At the levels used to record the stimulus on the tape, no cross recording was found on the channel upon which the response at the round window was recorded. Furthermore, in those cases in which there was no response, tones could not be detected on the response channel using a band pass filter.

Seventeen patients have been investigated under general anesthesia. There are eleven cases of tympano-mastoiditis, five of otosclerosis and one of congenital neurosensory deafness.

Note on Illustrations. Figures 11, 12, and 13 were made without using a filter. Figure 14 was made by setting the Kronhite Variable band pass filter type 310 AB at 20 to 1,000 cycles per second in series with the playback of the tape recorder thus limiting the observable

TABLE II

DETAILED RESULTS OF 16 PATIENTS ON WHOM AN ATTEMPT WAS MADE TO RECORD COCHLEAR POTENTIALS

Frequency (cps)		125	250	500	1000	2000	4000	8000	CLICK
Dynes/cm^2			3	4	5	5	3	1	0.2
CASE NO.	DIAGNOSIS								
1*	Tympanomastoiditis	Excellent cochlear potential to whistle. Greater than 20.0 μv.							
2*	Tympanomastoiditis	Minimal response. Possible puncture of round window membrane.							
3*	Tympanomastoiditis	80 db loss. No response attainable.							
4*	Tympanomastoiditis	20 and 30 μv response to 435, 512, 1000 and 2000 cps.							
5†	Otosclerosis	9 μv	5 μv	6 μv	15 μv	17 μv	63 μv		50 μv
6†	Tympanomastoiditis	50 db loss. No response attainable.							
7†	Tympanomastoiditis	Less than 1 μv at 1000 cps.							
8	Tympanomastoiditis	No response attainable.							
9	Otosclerosis		2.5 μv	3.5 μv	2.0 μv	3.5 μv	2.3 μv	6.0 μv	35.0 μv
10	Otosclerosis		1.5 μv	3.0 μv	4.0 μv	8.0 μv	5.0 μv	4.0 μv	50.0 μv
11‡	Tympanomastoiditis		7.5 μv	6.0 μv	8.0 μv	10.5 μv	15.0 μv	10.0 μv	0
12	Tympanomastoiditis		5.5 μv	5.0 μv	4.0 μv	4.5 μv	4.0 μv	3.0 μv	0
13	Congenital neurosensory deafness		0	0	1.5 μv	1.5 μv	1.5 μv	1.5 μv	0
14§	Tympanomastoiditis		+	+	+	+	+	+	0
15	Otosclerosis		1.5 μv	1.0 μv	1.0 μv	10.0 μv	9.0 μv	3.0 μv	50.0 μv
16	Tympanomastoiditis		0.5 μv	1.5 μv	0.5 μv	1.0 μv	1.5 μv	1.0 μv	0

* Reported in detail Ref. No. 7.

† Stimulus intensity does not pertain.

‡ After mobilization of stapes from scar tissue.

§ + = recording present. No calibration.

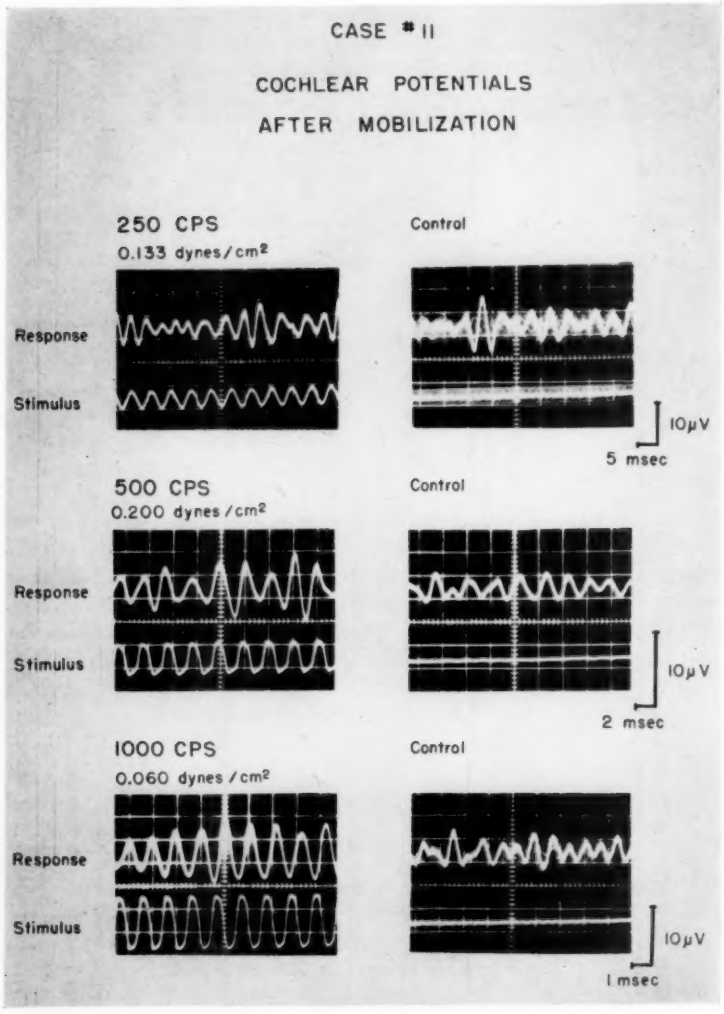

Fig. 9.—Case 11 (tympano-mastoiditis). Cochlear potentials obtained for 250, 500, and 1,000 cycles per second after mobilization of stapes from scar tissue. Note difference in the microvolt scale from Figure 7.**

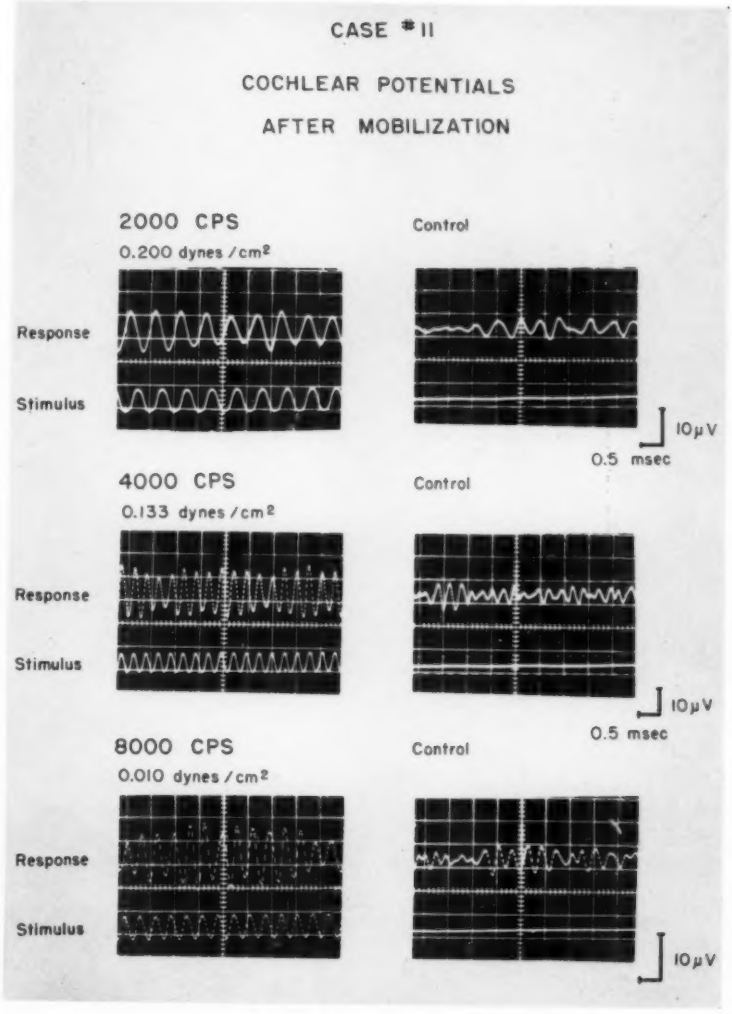

Fig. 10.—Case 11 (tympano-mastoiditis). Cochlear potentials obtained for 2,000, 4,000, and 8,000 cycles per second after mobilization of the stapes from scar tissue. Note the difference in the microvolt scale from Figure 8.**

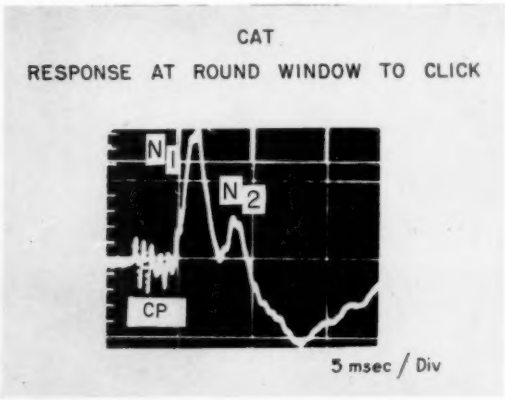

Fig. 11.—The response at the round window in the cat to a click. Note the CP, cochlear potential, and the two parts of the action potential of the VIII nerve, N_1 and N_2. Negative deflection is up.

band pass. The remaining figures were made with the band pass filter set to be 3% of the observed frequency. The control in Figures 3, 4, 7, 8, 9, and 10 is that period between two stimuli when there was no stimulus. The tape recorder was still recording and the pictures are taken at the same band pass filter settings as with the tones.

FINDINGS

Table I summarizes the results of the 17 cases. In the 11 cases of tympanomastoiditis cochlear potentials were recorded in low tones in 6 and in the high tones in 7. There was one positive response to click in the 6 recordings attempted.

Low tones were recorded in 4 out of 5 of the cases with otosclerosis. High tones were recorded in all of the cases. Four out of the 5 gave a good response to a click stimulus.

The case of congenital neurosensory deafness responded only at the high tones. No click response was noted. In this case a thin secondary membrane was found in the round window niche, which

may have interfered with a good contact between the electrode and the true round window membrane. The results with the exception of Case 17 are tabulated for the entire series in Table II.

Response to Tone. A set of cochlear potentials are demonstrated in Case 5, otosclerosis, Figures 3 and 4. As the stimulus is reduced in 10 decibel steps from an arbitrary zero, the potential also falls. At 125 cycles per second at 0 decibels there was a 9 microvolt cochlear potential; at minus 10 decibels there was a 6 microvolt response. At 250 cycles/second, at the 0 decibel level, there was a 5 microvolt response. Using 500 cycles per second at 0 decibels there was a 6 microvolt cochlear potential and at minus 10 decibels 4 microvolt response. At 1,000 cycles per second there was a 15 microvolt respone at 0 decibels, at minus 10 decibels a 7 microvolt response, and at minus 20 decibels a 5 microvolt cochlear potential. At 2,000 cycles per second with 0 decibels there was a 17 microvolt response, and at minus 10 decibels an 8 microvolt cochlear potential. At 4,000 cycles per second at the 0 decibel level, there was a 63 microvolt cochlear potential, which is the largest potential recorded. At minus 10 decibels there was a 14 microvolt cochlear potential. The cochlear potentials in the other cases show a similar decrease in amplitude with the decrease in stimulus intensity. In some instances response was not obtained at the lower levels of sound intensity.

Cochlear potentials were obtained from an anesthetized cat using the same technique and equipment. In the cat (Fig. 5) with an intact tympanic membrane and ossicular chain, there were large cochlear potentials. After myringotomy there was a substantial decrease in the cochlear potential at all frequencies except 250 and 4,000 cycles per second. Following the myringotomy the crura of the stapes were separated from the foot plate. This resulted in a profound loss of the cochlear potential at all frequencies except 2,000 cycles per second. At 2,000 cycles per second there was an increase in the cochlear potential.

Comparison of the cat's cochlear potential after myringotomy and disarticulation of the crura of the stapes and that of four cases using the same stimuli are seen in Figure 6. It is noted that the cat has moderately larger responses than man in the 250, 500 and 1,000 cyles per second range. At 2,000 cycles per second the response is much greater than in the human being. In the high frequencies,

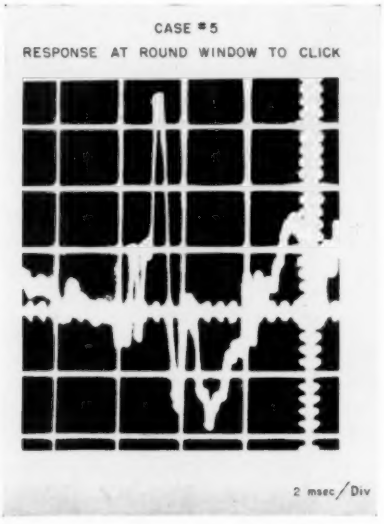

Fig. 12.—Case 5 (otosclerosis). The response at the round window in man to a click. Note the similarity to Figure 11. There is a definite cochlear potential followed by two slow waves, the N_1 and N_2 of the action potential of the VIII nerve. Negative deflection is up.

4,000 and 8,000 cycles per second, the response in the cat is the same as or less than the cochlear potential of the human cases.

Recordings were made in Case 11 during the second part of a type IV tympanoplasty. The recordings were made before the oval window was explored. Then another series of recordings was made after the foot plate of the stapes was mobilized from the scar tissue in the oval window (Figs. 8, 9, 10 and 11). The results show that at 250 cycles per second before mobilization there was a 3 microvolt cochlear potential and after mobilization a 7.5 microvolt response; at 500 cycles per second a 2.5 microvolt response before and 6 microvolt cochlear potential after; using 1,000 cycles per second a 3.7 microvolt response before and 7.5 microvolt cochlear potential after; at 2,000 cycles per second a 2.1 microvolt response before and 10.5 microvolt response after mobilization; at 4,000 cycles per second a 2.8

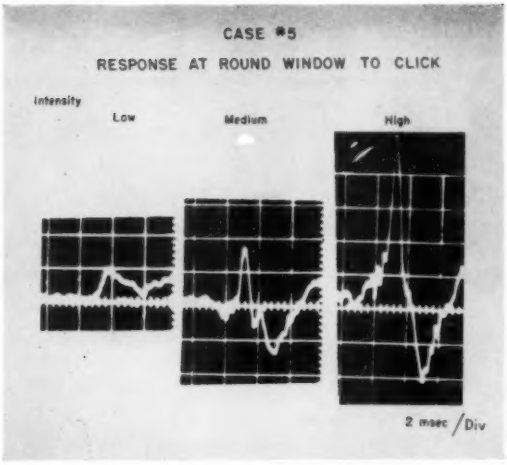

Fig. 13.—Case 5 (otosclerosis). The response at the round window to a click of varying intensity. At the low intensity there is only a single slow wave. Using the medium intensity both the N_1 and N_2 are seen. The high intensity increases the amplitude of the cochlear potential and the segments of the action potential of the VIII nerve. Negative deflection is up.

microvolt response before and 15 microvolt cochlear potential after mobilization; at 8,000 cycles per second a 2.1 microvolt response before and 10 microvolt cochlear potential after mobilization.

Response to Click. The response at the round window to a click stimulus in the cat was described by Derbyshire and Davis in 1935.[2] In the cat this consists of the cochlear potential and the action potential of the VIII nerve (Fig. 11). The action potential of the VIII nerve is divided into an N_1, the first slow potential, and the N_2, the second slow potential. The total duration of both is about 5.0 milliseconds. On occasion, an N_3 is also seen. When a click was presented to the human ear, a similar configuration was recorded (Fig. 13). The cochlear potential is followed by two slow waves, the N_1 and N_2 with a total duration of about 4.5 milliseconds. When the stimulus intensity of the click is increased from a low level to a high level, the change in the action potential in man is similar to the cat (Fig. 13).

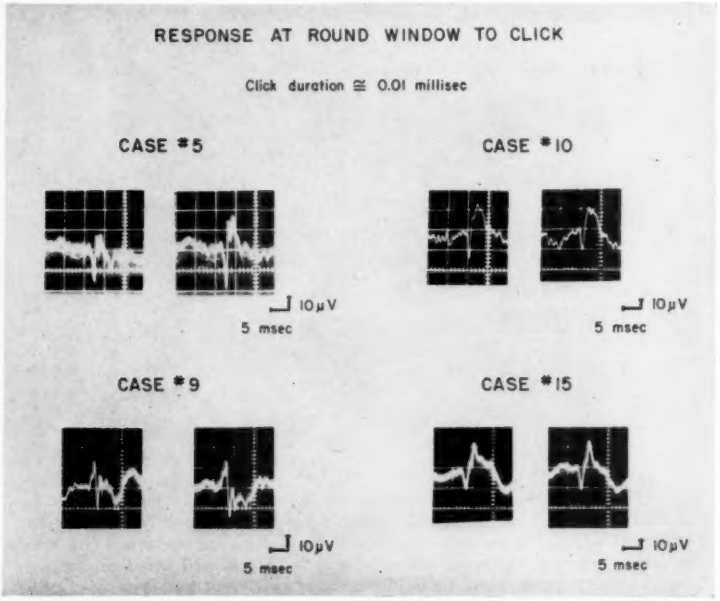

Fig. 14.—Cases 5, 9, 10 and 15. The response at the round window to click in four cases. Two different responses are shown for each case. Note the similarity in duration, wave form, and amplitude. The negative deflection is down.

At the low level only one wave appears, presumably the N_1. The N_2 appears only after a more intense stimulus is used. The response to clicks in four cases are illustrated in Figure 14. They are all of a similar configuration, duration, and amplitude. Case 5 had a response of 50 microvolts; Case 9, 35 microvolts; Case 10, 50 microvolts; and Case 15, 50 microvolts. The duration of the entire action potential in the four cases is about 4.5 milliseconds. The N_1 is always larger than the N_2. The N_1 has a duration of 2 milliseconds and the N_2 of 2.5 milliseconds.

In Cases 9, 10, and 15 the stimuli were presented so that a single click was presented every 20 seconds. Then a pair of clicks 100 milliseconds apart were presented every 20 seconds. In this group there

was no difference in the size of the first N_1 and N_2 as compared to the second N_1 and N_2. The two action potentials were 100 milliseconds apart. Then a series of three clicks 100 milliseconds apart were presented every 20 seconds. Again the time between clicks remained the same and the size of the three action potentials were similar.

This series was repeated with 50 milliseconds between two clicks. They were presented every 20 seconds and then three clicks with 50 milliseconds between each click every 20 seconds. There was no difference in the amplitude of the action potentials and the time between action potentials was the same interval as was between the stimuli.

When the time between two clicks was shortened to 20 milliseconds and they were presented every 20 seconds, the amplitude of the second action potential was reduced 20 per cent. The time between responses was 20 milliseconds, the same as between the stimuli. When three clicks, with 20 milliseconds between each click, were presented every 20 seconds, the third action potential was of the same size as the second, i.e., 20 per cent less than the first. The time between responses did not change. The findings were similar in all four cases.

COMMENT

Round window recordings have been made in seventeen patients. In 13 of the 17 cases measurable cochlear potentials have been recorded. In the cases in which the sound pressure was calibrated, it was noted that in man the greatest cochlear response was obtained at 2,000 to 4,000 cycles per second. This is in agreement with the audiometric testing of such patients with middle ear disease. The animal experiments demonstrated that the human cochlear potential in the 4,000 to 8,000 cycle per second range was of a similar magnitude to that of the cat after the tympanic membrane and the ossicular chain were damaged.

The results of the human cochlear potentials vary somewhat from case to case. It is assumed that in the cases of otosclerosis the cochlea and the round window membrane are not damaged. The difference in the response in the various cases may lie in the degree of contact of the electrode with the round window membrane and in the severity of otosclerotic involvement. During surgery much time has been

spent in gaining access to the round window membrane, in reflecting any pseudomembrane, and in removal of granulation tissue from the niche. The best human recordings are obtained when the electrode is placed directly on the round window membrane.

It is of interest to note that after the mobilization of the stapes foot plate from scar tissue, there is an increment in the magnitude of the cochlear potential. This would seem to confirm the validity of the findings.

The response to click stimuli in man is essentially the same as in the cat. It is assumed that the action potential of the VIII nerve is being recorded from the round window membrane in man. The click response in man follows the same growth pattern with increased intensity of stimuli as is known in the cat. The response in the four cases of otosclerosis were all similar.

SUMMARY

1. Cochlear potentials in man are readily obtainable.

2. An increase in the cochlear potential resulted from the mobilization of the foot plate of the stapes which was bound down by scar tissue.

3. Round window response to a click was recorded in man and found to be similar to the action potential of the VIII nerve in the cat.

4. Equipment for stimulating and recording cochlear potentials in the operating room has been described.

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XLI

SOME PHYSIOLOGICAL FACTORS IN INNER EAR DEAFNESS

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As our knowledge of the anatomy and physiology of the ear increases, the terms used to describe types of deafness need revision. The terms that are used are generally meant to convey some information about the locus of the lesion causing the hearing loss. Thus the term cochlear or inner ear deafness refers to changes in that part of the ear where the vibratory energy within the fluids is converted into nerve impulses. And we now know, on the basis of years of research, that the structure responsible for this transformation is the organ of Corti; specifically it is the hair cells.

There was a time when it was thought that the nerve fibers were stimulated directly by mechanical vibration. In 1683 DuVerney,[1] who did not know there was fluid in the inner ear, guessed that the nerve fibers were spread out on one side of the spiral osseous lamina, and that stimulation was brought about through the resonant vibration of various parts of this bony structure in response to aerial vibrations transmitted into the ear.

Even Corti,[2] who clearly observed the hair cells, thought their action was a purely mechanical one. Through the action of vibrations within the fluids of the inner ear these cells supposedly were made to beat like drumsticks upon the membrane over which were stretched the nerve fibers. This mechanical beating presumably gave rise to the nerve impulse.

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Helmholtz,[3] who described the hair cells and mentioned that fine nerve fibers passed among them, described the nerves as terminating in a "peculiar auxiliary apparatus" which could be put into sympathetic vibration by vibrations entering the ear. Through general agitation the nerves were then excited. The hair cells received credit for being important structures but their role was described as merely auxiliary.

In 1892 Gustav Retzius[4] suggested the proper function of the hair cells, that they are the final receptors for vibration and that the nerve fibers receive their stimulation from these cells.

The eventual recording of the electrical effects of the cochlea by Wever and Bray[5] and the subsequent research that has led to the observation that it is vibration of the sensory cells that gives rise to this cochlear alternating current response has led to a more complete understanding of the transducer action of the sensory cells. As a technique, the recording of these electrical potentials has been used for two purposes: one as an indicator of auditory activity in response to sound as the ear is altered experimentally somewhere along the pathways of sound conduction to the sensory cells, and another as an indicator of hair cell function as these cells respond to sound vibration. The response of the sensory cells varies with the magnitude of the vibrations reaching them and reflects all processes involved in this transfer of sound energy up to the actual generation of the electrical potential. The transformation of mechanical vibration into an electrical potential is a property of the hair cell and presumably the magnitude of the potential also depends upon the health of the sensory cell.

Interference with the vibration-conducting pathways gives rise to what is described as a conductive deafness, while alterations within the environment of the sensory cells that diminishes their ability to perform, produces a cochlear or inner ear deafness. These two types of hearing loss can be diagnosed audiometrically but for experimental purposes the recording of the cochlear potentials is the best index of sensory cell function. Studies of these potentials have been concerned with two aspects of their behavior: one on the nature of the potentials themselves in response to differing frequencies and magnitudes of sound, and another on the characteristics of the response as changes are produced within the hair cells.

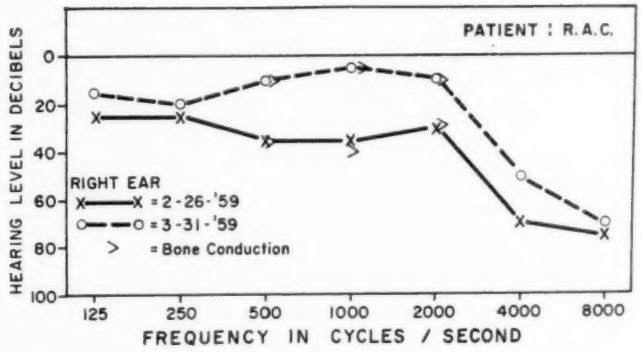

Fig. 1.—Recovery of hearing in a patient after treatment for hypothyroidism.

In pursuance of studies concerned with the nature of the response itself the distribution of energy along the basilar membrane in response to tones of different frequencies has been worked out[6,7] and found to agree with similar interpretations made by visual methods.[8] In addition to this, several of the characteristics of this response to sounds of increasing intensity have been observed. There is, for low-level sounds, a directly proportional increase in the electrical response with increasing sound intensity. At high levels this correspondence ceases and the increases in cochlear output become less and less until a maximum is reached. Beyond this point the responses drop off and injury to the sensory cells results. Both for intensity and duration of the stimulating tone there is a point where the response suddenly drops.[9] After this has occurred the input-output function of the inner ear changes in shape, in slope and in maximum output. Further studies of the response of the inner ear to high-intensity sounds[10] show the harmonic content of the response to be very high during the duration of intense sounds and that, if no injury has occurred, the nature of the response is independent of the rise time of the tone.

Those experiments which have used the cochlear response as an index to changes produced within the sensory cells have demonstrated that excessive vibration or change in the fluid environment that are

detrimental to the sensory cell produce a lowering of the electrical response. And it is generally assumed that such a decrease in response would be detectable audiometrically but the frequency pattern of loss measured audiometrically and electrically would not be expected to correspond very closely.[11-13] In addition to the investigations of the characteristics of the alternating-current response of the sensory cells to test tones under various inner ear conditions, we have, in our laboratory, been studying the effects of overstimulation and internal factors on the function of the sensory cells with the hope of determining the conditions necessary for relieving inner ear deafness. These studies involve the cochlear potentials as the measure of inner ear function as various physiological conditions of the sensory cells are altered experimentally. I would like to present some results from studies on the changes in inner ear function as the result of hypothyroidism and disruption of the intralabyrinthine fluid physiology.

HYPOTHYROIDISM AND DEAFNESS

Dr. Ritter and I[14] recently reviewed the question of deafness that is often associated with either congenital or acquired hypothyroidism. Although there has been some debate as to whether this deafness is conductive or cochlear it is generally conceded to be the latter, but the nature of the lesion and its exact locus have never been described. Two cases in the otology clinic at the University of Michigan had been seen and examined audiometrically. The deafness was definitely cochlear and it was found that the administration of thyroid in one instance and the cessation of a thyroid inhibiting compound in another brought on an improvement in hearing.

Figure 1 shows the before- and after-treatment audiograms of one of the patients. There was a history of employment in high noise levels which may account for the persistent high-tone loss. In the region of 500, 1000 and 2000 cps the improvement in hearing amounts to as much as 30 db.

In order to investigate the nature of the lesion causing this reversible type of deafness we decided to use the chick because of the ease of working with the embryo. Fertile eggs were divided into three groups: one group was allowed to develop normally, one group was injected with 2 mgs of thiourea in ½ cc of chicken ringers, and one group was injected with ½ cc of plain chicken ringers. The chicks

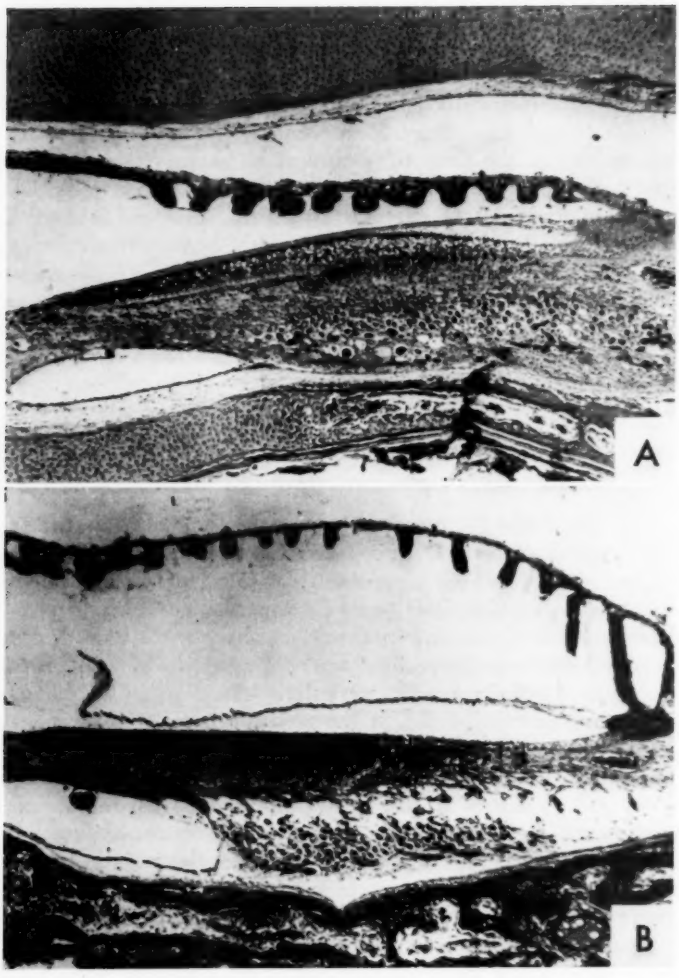

Fig. 2.—*A.* The acoustic papilla of a chick injected on the fourth day of incubation with 2 mgs thiourea in ½ cc of chicken ringers. There is a prominent region of edema between the hair cells and their supporting cells. The encroachment of this edema upon the hair cells has caused them to become misshapen. *B.* The acoustic papilla of a normal chick. This structure is unlike the organ of Corti of animals in that there are no rods of Corti nor are there any Deiters' cells. The supporting layer consists only of a continuous row of columnar cells.

were sacrificed on the 21st day, the normal day of hatching, and processed for histological examination. Only those embryos injected with thiourea on the 4th day of incubation showed any abnormality of the ear.

Except for some delay in the calcification of the stapes no distinguished abnormality of the middle ear was observed. In the inner ear there appeared a distinct layer of edema between the hair cells and the supporting cells. Figure 2 shows photomicrographs of both the normal chick acoustic papilla and the acoustic papilla of a hypothyroid chick. It can be seen that the chick sensory area differs considerably from that of the human. There are no rods of Corti nor are there any Deiters' cells. It is conceivable, though, that something similar to the edema produced in the chick organ of Corti could be produced in the human. The decrease in sensitivity may be caused by the pressure of this edema upon the sensory cells. In Figure 2A the edematous layer has encroached upon the sensory cells so that they are misshapen and tooth-like in appearance. It is also possible that this condition would be reversible.

To check further upon the nature of this hearing loss in hypothyroidism we are conducting further studies on the histological changes correlated with the changes in electrical output of the cochlea.

The thiourea injected chicks are invariably delayed in hatching and many are never able to do so. Those that do hatch are very weak and scrawny and sometimes must be force fed. Some preliminary results show the electrical changes that take place within the cochlea of these chicks as the result of the hypothyroidism and also as the result of subsequent treatment with thyroid.

Figure 3 shows the electrical audiograms of two different chicks that were both hatched in a hypothyroid condition. Their history is as follows.

Chick 377. On the fourth day of incubation this fertile egg was injected with 2 mgs of thiourea and incubated continuously until hatching on the twenty-fourth day (3 days delayed). At the time of hatching the chick was weak and underdeveloped. Feather development was delayed and spotty. Force feeding was necessary for 24 hours until the chick had enough strength to peck at his food. On

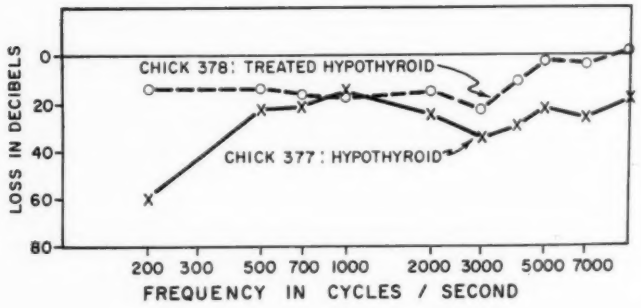

Fig. 3.—The electrical audiogram from two chicks injected on the fourth day of incubation with 2 mgs of thiourea in ½ cc of chicken ringers. Following hatching one chick (377) remained untreated and the other received 6 mgs of thyroid in 30 ccs of drinking water from the eleventh to the fifteenth day. The electrical audiogram was taken on the fifteenth day after hatching.

the eleventh day the chick was anesthetized with urethane and the middle ear exposed. A small needle electrode was placed on the epithelial lining of the middle ear directly over the endolymphatic projection that serves as the round window. The electrical audiogram is shown as the solid line in Figure 3.

Normal chicks of the same age were operated on and recorded from in the same way. Comparison of electrical responses from the experimental chicks with those of the normal are the basis of the audiograms.

Chick 378. This fertile egg was injected on the fourth day of incubation with 2 mgs of thiourea and incubated continuously until hatching on the twenty-fourth day. This chick was from the same batch of eggs as chick 377. At the time of hatching this chick was also weak and scrawny and had to be force-fed for 24 hours. On the eleventh day after hatching, thyroid in the amount of 6 mgs in 30 cc of water was administered to the chick through his drinking water. Within 24 hours the chick showed increased activity, gained weight and began to feather more completely. Four days later this chick was

operated upon in the same manner as the others and an electrical audiogram taken. This is shown as the dashed line in Figure 3.

The ears of these chicks have all been saved for histological examination.

Because the same chicks are not used for both the hypothyroid and the treated hypothyroid measures many chicks are needed. These results reported here demonstrate the experimental methods of determining both morphological and functional changes in experimentally produced hearing loss.

The important observation is that this type of deafness is reversible, at least in some instances, and the important question concerns the part played by the thyroid hormone in the development of the auditory organ as well as in the maintenance of its normal function.

INTRALABYRINTHINE FLUIDS AND DEAFNESS

During the course of our investigations on stimulation deafness it has been found that, associated with permanent loss of hearing in experimental animals, there is or had been at one time a rupture of Reissner's membrane. The kind of experimental deafness discussed here is that produced by extremely loud sounds for a short period of time. Deafness produced by moderately loud sounds over a period of years is probably the result of cumulative mechanical damage to the sensory cells and may not be the same as that discussed here.

In order to illustrate the point I wish to bring out here I have selected two animals from a group of nine that were stimulated by a white noise of 136 db over-all sound pressure level for 20 minutes.[15] Cochlear potentials were recorded on these animals before stimulation, immediately after stimulation and again after two months in quiet. In all, severe losses in cochlear responses were produced immediately afterwards, some more severe than others, but the differences in losses were not nearly as great as that found among the same animals two months later. About 60 per cent of the animals showed improvement, 10 per cent remained the same and 30 per cent showed a further loss in sensitivity.

Examples of this are shown in Figures 4 and 5. Figure 4 shows electrical audiograms from a guinea pig (GP 49R) that showed a fur-

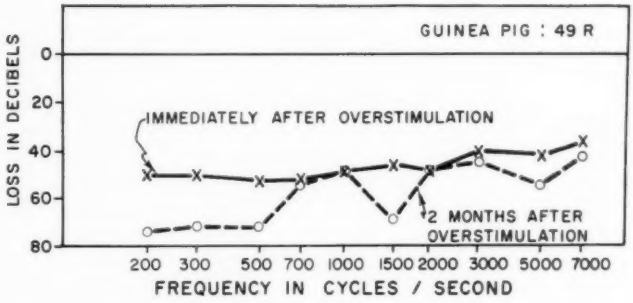

Fig. 4.—Electrical audiograms from a guinea pig (49R) stimulated with 136 db of white noise for 20 minutes. There is a further loss in electrical output two months after the overstimulation.

ther decrease in inner ear function during the two months allowed for recovery after the overstimulation. The loss in response immediately after overstimulation was quite flat at 50 db except for the higher frequencies where it was somewhat less. Two months later the sensitivity had decreased considerably for the lows and highs but not so much for the middle frequencies. There was, however, no improvement in response at any frequency.

In another anmial (GP 48R) that was stimulated by exactly the same amount of noise and in exactly the same manner, the loss in response immediately after overstimulation appeared to be almost identical to that of the animal shown in Figure 4. Figure 5 shows the electrical response curves for this second animal; again the initial loss is around 50 db. It is even greater by 2-4 db in the middle range than that of the first animal. Two months later this ear shows a remarkable recovery. Only for 500 and 700 cps is the loss greater than 10 db and for the higher frequencies it is practically normal.

Since all of the animals in this series were subjected to the same noise under conditions that were as carefully controlled as possible, an interesting question arises as to why recovery should not be more or less alike in all of these animals.

One possibility is that the structures of the organ of Corti vary from animal to animal in their innate fragility; somehow the loud

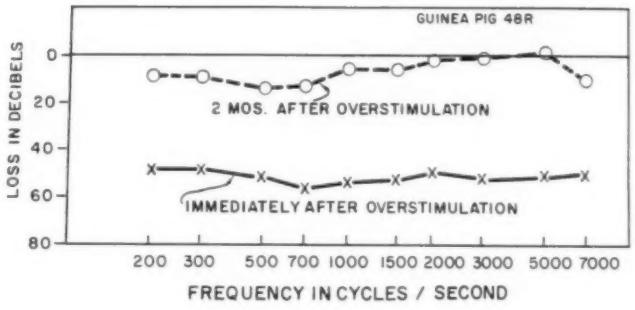

Fig. 5.—Electrical audiograms from a guinea pig (48R) stimulated with 136 db of white noise for 20 minutes. There is almost complete return to normal of electrical output two months after the overstimulation.

sounds can be more destructive to some ears than to others. But an argument against this is that the range of hearing losses is much greater after two months of recovery than it is immediately after the overstimulation.

Another possibility is that the problem of individual differences in susceptibility to noise induced hearing loss is primarily one of the ear's ability to recover from an acoustic insult rather than one of structural weakness. The supposition is that either the animal's constitutional factors are such that chemical elements necessary to replenish something broken down or used up by the overstimulation affects the fluid physiology of the inner ear in such a way that certain repair processes have to take place before the normal situation is reestablished.

Misrahy[16] has suggested that the overstimulation changes the permeability of the basilar membrane so that there may be a leakage of potassium ions from the scala media into the scala tympani thus impairing the activity of hair cells or nerve endings. Histological examination of the two guinea pig ears of our series described above reveals that the rupture or non-rupture of Reissner's membrane may have much to do with the recovery of function following acoustic overstimulation.

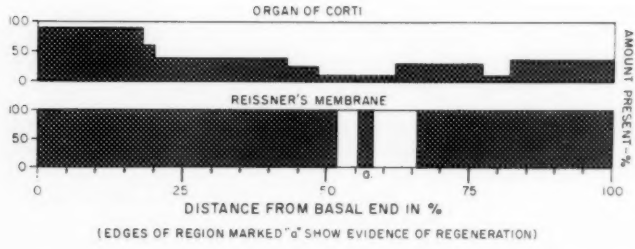

Fig. 6.—Linear plot of the organ of Corti and Reissner's membrane from the guinea pig of Figure 4 (49R). From the point at 20 per cent of the distance from the basal end of the basilar membrane all the way to the apex there is less than 50 per cent of the organ of Corti present. Reissner's membrane is ruptured in the region of maximum damage to the organ of Corti.

Linear plots of the organ of Corti of these animals were made from graphic reconstructions of the cochleas made from serial sections of the temporal bones.

Figure 6 shows the plots for guinea pig 49R, the electrical audiograms of which are shown in Figure 4. Although there are evidences of repair in Reissner's membrane there are still regions where the membrane is torn or missing. In this region the organ of Corti has practically disappeared and in fact appears non-functional in all regions above about the 20 per cent point along the basilar membrane. This ear showed a further loss in electrical response during the two months following the overstimulation.

Guinea pig 48R on the other hand shows in the linear plot of Figure 7 no breaks in Reissner's membrane and very little damage to the organ of Corti. As the electrical audiograms of Figure 5 show the function of this ear returned almost to normal during the two months following the overstimulation.

Both of these ears showed practically the same amount of functional loss immediately after overstimulation but were 40 to 50 db apart two months later. Could it be that the break in Reissner's membrane of guinea pig 49R allowing perilymph to surround the

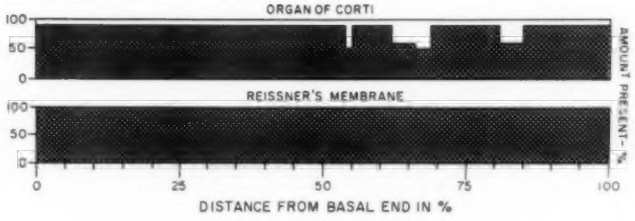

Fig. 7.—Linear plot of the organ of Corti and Reissner's membrane from the guinea pig of Figure 5 (48R). The organ of Corti is in good condition for the entire length of the basilar membrane and there are no breaks in Reissner's membrane.

injured organ of Corti was responsible for the failure of this ear to recover its function?

Dr. McCabe and I[17] have suggested that the same process may operate in the fluctuating hearing loss associated with Ménière's disease. The increased endolymphatic fluid may cause Reissner's membrane to break allowing perilymph to impair the function of the organ of Corti. The membrane may repair itself following the temporary relief from the increased pressure allowing some recovery of function. As the pressure again builds up Reissner's membrane may break once more to be followed by subsequent repair. This repeated process eventually obliterates the scala media and normal function of the organ of Corti is completely lost.

Such a theory requires the assumption that the hair cells of the organ of Corti are bathed by endolymphatic fluid and that because of its different chemical make-up perilymph, if allowed to come in contact with these cells, impairs their function. This runs counter to the conclusions that Tasaki, Davis and Eldredge[18] have reached that the organ of Corti is actually a part of the scala tympani and that the membrane separating the perilymph of the scala tympani from the endolymph of the scala media is not the basilar membrane but is the reticular membrane which is the supporting structure for the hair-bearing ends of the hair cells. This view is based on the idea that endolymph, high in potassium, would, if present around the hair cells

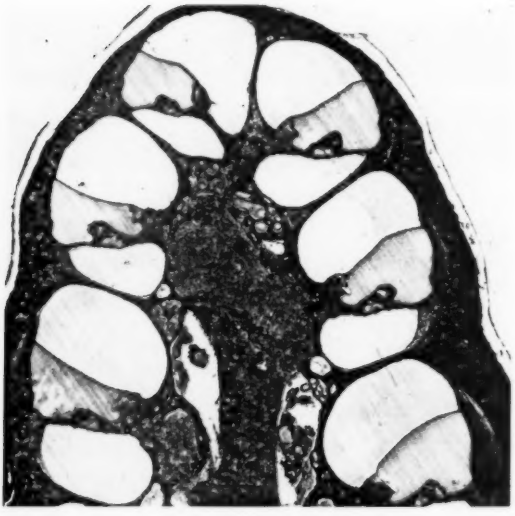

Fig. 8.—A mid-modiolar section of the cochlea from the guinea pig of Figures 5 and 7 (48R). Special stain darkens the endolymphatic spaces which are seen to include the entire organ of Corti to the basilar membrane. Perilymph from the scala tympani is excluded from the scala media and organ of Corti by the basilar membrane and perilymph from the scala vestibuli is prevented from entering the scala media by Reissner's membrane.

and their associated nerve fibers, surround the sensory endings with more than enough potassium ions to abolish the electrical responses completely.

Obviously it is important to know whether the hair cells are surrounded by perilymph or endolymph if we are to account for some forms of inner ear deafness as being caused by perilymph invading the scala media from the scala vestibuli through a break in Reissner's membrane. If it were possible somehow to make endolymph appear different than perilymph then histological study might show which fluid pervades the organ of Corti. We have worked on this notion for some time and through chance have found a process that stains the celloidin used for mounting the tissues darker in the endolymph-

Fig. 9.—A section of the cochlea from the guinea pig of Figures 4 and 6 (49R). The special stain darkens the endolymphatic spaces except in the region of the break in Reissner's membrane where perilymph and endolymph are allowed to mingle. The distinct barrier (basilar membrane) between scala media and scala tympani is obvious. If perilymph surrounds the organ of Corti, as proposed by some investigators, it should have access to the scala media upon disruption of the organ of Corti by loud sounds as in this ear, but perilymph is clearly excluded from the scala media by the basilar membrane.

atic cavities than in the perilymphatic cavities. We have used this method in staining some miscellaneous sections from the overstimulated ears of guinea pigs 48R and 49R.

Figure 8 shows a mid-modiolar section from the ear of guinea pig 48R whose electrical audiogram and linear plots were described above. The endolymph stains dark and the tunnel space and organ of Corti all take on this dark appearance. There is no indication that

the reticular membrane is the dividing tissue; the demarcation between scala media and scala tympani is clearly defined along the basilar membrane.

As was shown in Figure 6 Reissner's membrane in guinea pig 49R was broken and failed to repair. Figure 9 shows the appearance of a section from this ear when stained by this process. The organ of Corti has almost completely disappeared as a result of the overstimulation and the remnants of Reissner's membrane can be seen in the second turn. In the apical and third turns the scala media has stained darkly while the perilymphatic spaces remain light. The boundaries of the scala media are clearly marked by Reissner's membrane and the basilar membrane. If the reticular membrane were the boundary it would have been eliminated by the violent vibrations of the stimulating noise and perilymph should have flooded the scala media from the scala tympani. This apparently is not the case.

In the second turn Reissner's membrane is broken but the basilar membrane has remained intact. Here also the scala tympani is clearly defined but the staining characteristics of the scala vestibuli and scala media are now alike since the fluids have mingled.

In the basal turn just below the region of the break in Reissner's membrane the scala vestibuli has stained somewhat darker than in the upper turns. But the scala tympani is again clearly defined as being bounded by the basilar membrane and bony walls.

This still leaves open the problem as raised by Tasaki of how the hair cells and nerve endings can operate if surrounded by a solution high in potassium. Since it is apparent that they are, our suggestion, that the integrity of Reissner's membrane has an important function in inner ear deafness and recovery of the organ of Corti from physiological insult, is tenable, but it means a reinvestigation of some notions proposed by others.

SUMMARY

Inner ear deafness has been defined as the result of changes in the functional capacity of the organ of Corti, particularly the hair cells. Experiments have shown that these hair cells give rise to an electrical alternating-current potential when stimulated by sound and that any

element injurious to these hair cells causes a decrease in their electrical output. Such changes are presumed to be detectable audiometrically and a decrease in electrical output indicative of inner ear deafness.

The electrical output of the hair cells in response to sound has certain specific characteristics which have to be considered when these potentials are used as indicators of hair-cell malfunction. These characteristics have been carefully studied over the last few years and some are reviewed here.

Overstimulation and changes in the fluid environment can seriously affect the function of the hair cells. Some studies in overstimulation are reviewed here and two lines of experimentation dealing with changes in the fluid environment are presented.

Two cases of deafness associated with hypothyroidism that showed improvement in hearing following treatment for the hypothyroid condition are presented. The deafness in these cases was of the perceptive type. Experiments on chick embryos were described which were designed to reveal the locus of the lesion causing the loss of hearing. In the hypothyroid chick a zone of edema was found beneath and encroaching upon the hair cells so as to compress them and make them appear like tiny teeth. These changes were correlated with decreased electrical output in response to sound and some preliminary indications that this condition is reversible were described.

Instances in earlier experiments of rupture and repair of Reissner's membrane following overstimulation are reviewed and the possibility suggested that the integrity of this membrane is necessary not only for the proper function but for functional recovery after injury of the hair cells. When perilymph is allowed to mingle with endolymph and surround the hair cells they become unable to function in the normal manner. This observation makes it necessary to accept the idea that endolymph surrounds and pervades the organ of Corti not perilymph as proposed by Tasaki, Davis and Eldredge.[18] By use of special staining techniques, histological evidence is presented demonstrating that the boundaries of the scala media and its contained endolymph are the limbus, Reissner's membrane, stria vascularis, spiral prominence, external sulcus, basilar membrane and internal sulcus.

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XLII

DISTRIBUTION OF HEARING LOSS IN VARIOUS POPULATIONS

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AND

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Our search for valid audiometric data to study the relations of hearing loss to noise exposure has led us into many places. The multiplicity of relations predicates a broad coverage of the various populations involved. The innumerable variables involved require large samples to equate differences that exist within and among the samples as well as within and among the populations from which the samples are taken. Paradoxically the larger the samples are the greater the number of possible variables. Since it is impractical for us to obtain all the data ourselves we must use data obtained by others which still further complicates our problems because:

1. Different audiometers are used, whose calibration levels may or may not be known.

2. Different testers do the tests. Each has his or her own technique. In the field, audiometric techniques are almost as numerous as the persons who do audiometry.

3. Audiometric environments leave much to be desired in most cases.

4. Subject motivation is frequently poor.

It should be quite obvious then that inter- and intra-comparisons of these population samples present many difficulties if one is to draw any meaningful conclusions. When analyses of raw data are used with no thought of inter- and intra-sample differences the results are far

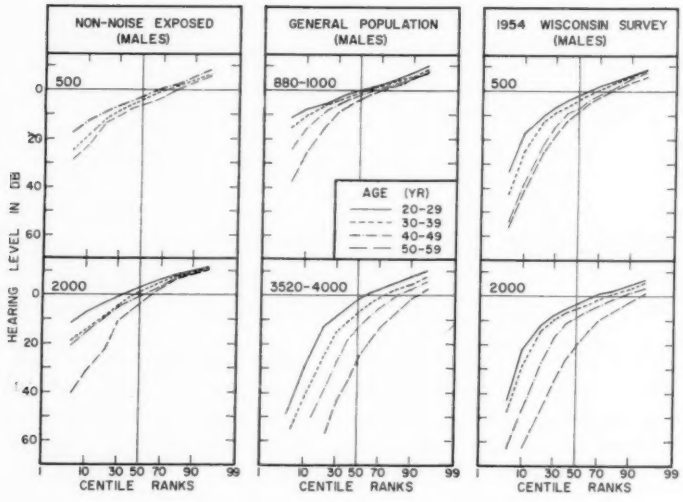

Figure 1

from logical. Since it is safe to assume that normal human hearing is relatively the same whether it is tested here or in Timbuctoo, we believe it is also logical to assume that comparable samples in respect to age and environment should show reasonably close agreement. When they do not, something must be done to equate the data. Just what to do was our problem.

Since the only factor common to all the samples is a "biological normal" we investigated the possibility of using this "biological normal" to equate our samples. What data would be satisfactory for use as a common reference? Obviously data from young ears should receive first consideration.

Perhaps the youngest group common to all our samples is the 20-29 year age group. A study of this group, however, showed changes in the higher frequencies, particularly 4000 c/s that were definitely related to noise exposure, either military or industrial. Even non-occupational noise exposure must be considered. If you will,

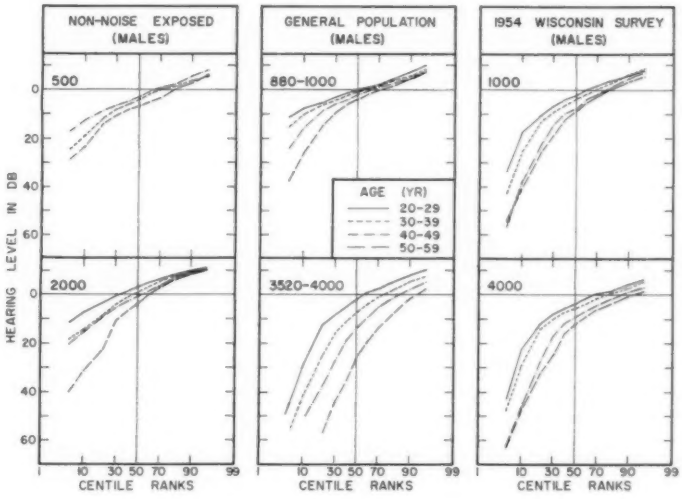

Figure 2

auditory wear and tear sustained during normally mechanized non-working hours. Because of the high threshold found at the high frequencies in the 20 to 29 year old groups, we decided to look at the thresholds in younger individuals. After comparing several groups between 17 and 19 we found group average hearing levels that varied as much as ten decibels. If our assumption that young otologically normal ears should not vary in excess of calculated statistical parameters from sample to sample is correct, and we believe it is, these variations must be due to confounding variables not related to the function of hearing; such as calibration, psycho-acoustic technique, test environment, and sample biases. On the basis of this assumption we believe that the threshold values found in 17 to 19 year olds can be used as reference levels to equate studies of auditory threshold data. We have found this method of equating our samples so satisfactory we include 17 to 19 year olds in all of the surveys we conduct in various plants throughout the country. The thresholds of the 17 to 19 year old samples are never used for these purposes unless there are at least 100 individuals in each 17 to 19 year old group.

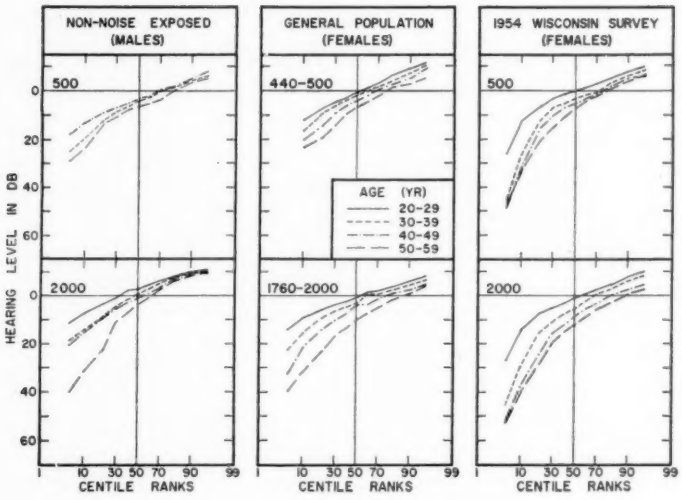

Figure 3

When the hearing level in the 17 to 19 year age group is used as zero for each related group the various population samples fall into logical order and we are able to make reasonable inter- and intra-comparisons whose differences can be ascribed to actual auditory threshold changes minimizing artifacts due to equipment, test environment or technique variables.

We are still a long way from success, however. We were (as everyone will be, did he but realize it) bothered by sample biases. Few of our samples were even close to being randomly selected. We are sure of only one.

Before population samples can properly be compared one must decide on how the data should be analyzed and displayed. This decision usually rests on what questions the data must answer. If we are satisfied with a simple comparison of average trends there is still the problem of choosing the central tendency statistic that best represents the average. Preferred descriptive statistics are based on the

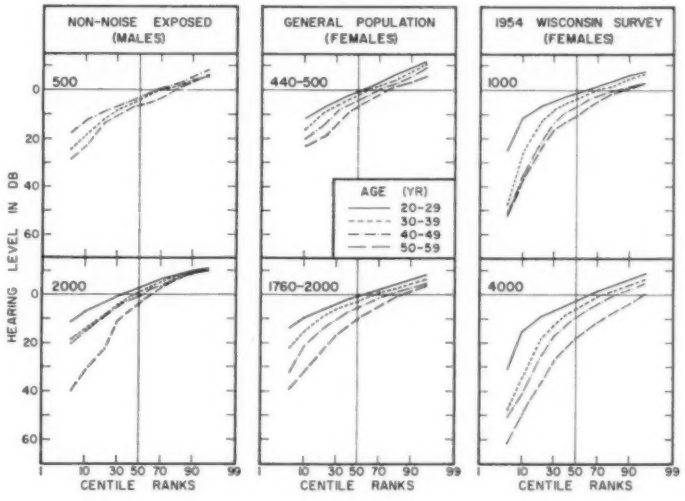

Figure 4

assumption that data are normally distributed. The most commonly used of these statistics are the means, standard deviations, and standard error of the means. The effects of skewing and truncation, which change the distribution from normal to non-normal and invalidate the use of preferred descriptive statistics are always present in audiometric data. Therefore it is better to use the median or the mode rather than the mean to describe the central tendency of non-normally distributed data.

Let us assume that we wish to determine the effects of relatively small differences in noise exposure or compare populations that are geographically different. We find that the modal or median differences are small and many times not statistically significant. Obviously if we are to determine differences between such samples some better method of data comparison must be employed. Knowing that some ears are more susceptible than others and that biological functions usually follow a normal distribution curve, that is, there are as many individuals on the better side of average as there are on the poorer side

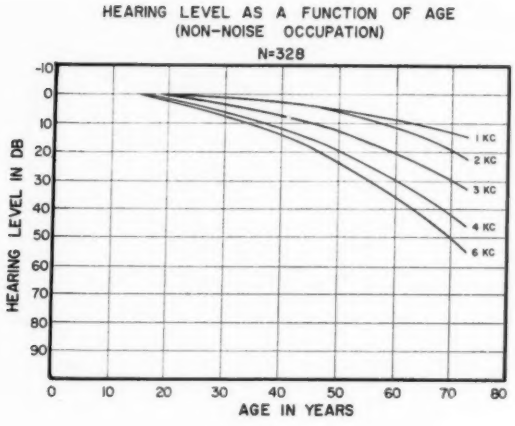

Figure 5

of average, we analyzed and distributed the data by centiles. Now let us examine some of the data displayed in this manner.

Much of our data was obtained from hearing surveys conducted at the World's Fair, the San Diego Fair, and the Wisconsin State Fair. These samples were obtained on a voluntary basis. No successful attempt was made to choose the respondents randomly. Consequently there is always the probability that many of the participants were interested because they either had a hearing loss or thought they had a hearing loss. This bias would tend to load the sample toward more hearing loss than would be found in a randomly selected sample.

The Wisconsin State Fair survey was conducted under the most careful supervision. There was no chance for the effects of audiometer problems, differences in psycho-physical techniques or bad environmental conditions to influence the data. Not only were all these conditions strictly controlled during the survey but careful cross comparisons between technicians, test booths and test instruments were made to check any possible effects of differences in these conditions (Fig. 1). There is little doubt in our mind that the data are valid and reflect the hearing acuity of the persons tested. When the

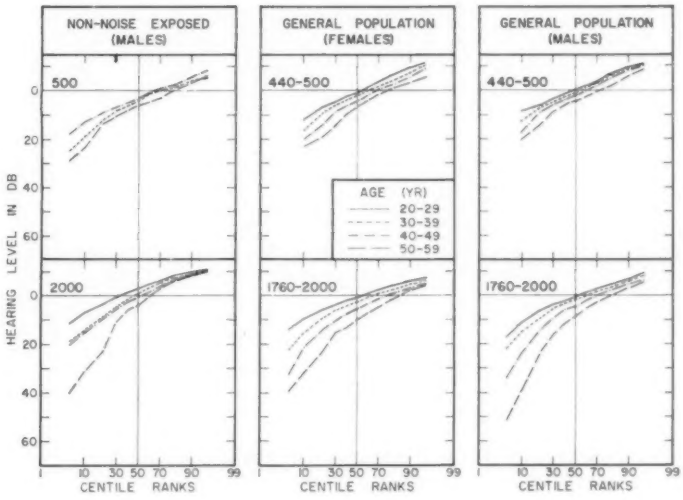

Figure 6

centile distributions of the various subgroups from the Wisconsin State Fair sample are compared with comparable groups from the World's Fair and San Diego Fair samples striking differences appear. The Wisconsin State Fair groups consistently show higher auditory thresholds. The explanation for this is not simple. All three Fair samples are made up of voluntary respondents. No successful attempt to randomize was made in any of the groups. The possibility of self selection because of hearing difficulty exists in each of these samples (Fig. 2).

Everything possible was done to determine the effect of self selection on the Wisconsin State Fair sample. All our efforts showed that the self selection bias was indeed present, but were the higher thresholds found due only to this bias? The World's Fair and San Diego Fair surveys must have included self selection biasing. Then why were the results from these two Fairs not the same as those from the Wisconsin State Fair survey? In our opinion there can be only one reason: there are more people in the Milwaukee area with hearing

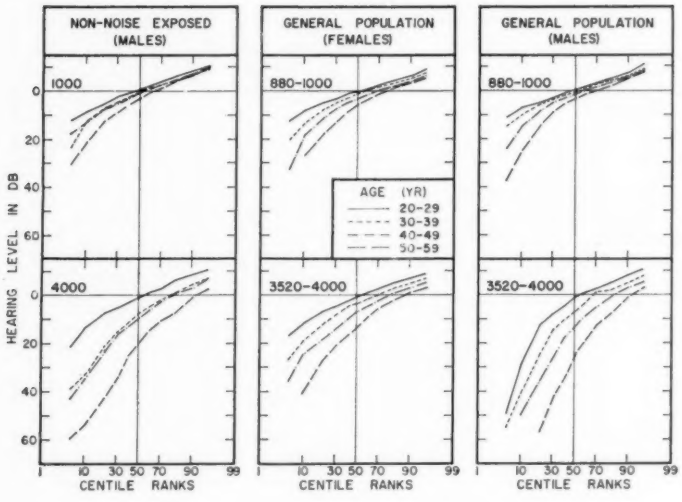

Figure 7

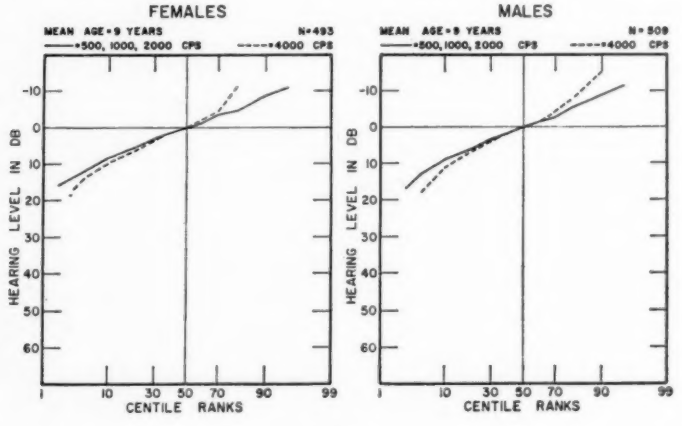

Figure 8

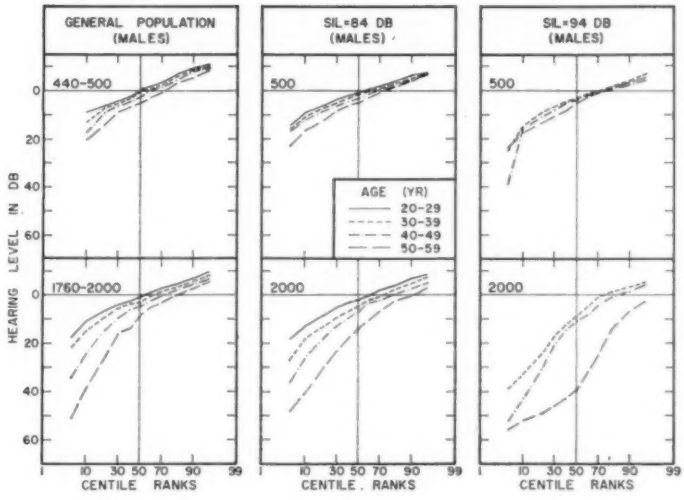

Figure 9

loss. In support of this statement we point out that Milwaukee is a heavily industrialized area and in the older age brackets (above 35) there are significantly more factory workers per unit of population than in the general population. As will be seen later, higher noise levels produce a proportionate increase in the number of persons with higher auditory thresholds. The higher the incidence of hearing loss the greater the effect of self selection toward higher hearing levels. Hence any extrapolations to the general population from the Wisconsin State Fair data would tend to overestimate the number of people with a hearing loss in the general population (Fig. 3).

Comparisons of the Wisconsin State Fair survey data will show consistently higher thresholds in the Wisconsin data. We are quite certain, however, that noise exposure does not explain the entire difference. The Wisconsin State Fair females show consistently higher thresholds, also (Fig. 4). Unless there is a greater proportion of female factory workers in Wisconsin there must be other explanations of the higher thresholds in addition to more noise exposure. Exam-

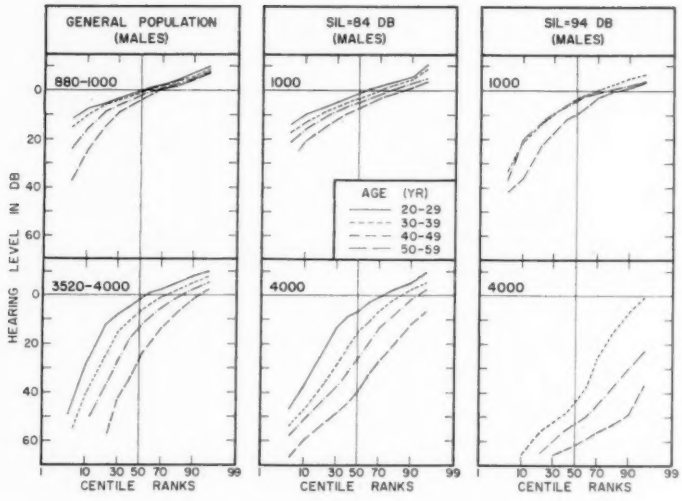

Figure 10

ination of the "office workers" in the Wisconsin sample show higher thresholds than any other "non exposed" group. Analysis of the noise exposure history of the office workers shows that only 10% of them could be called non-noise-exposed. Such data are further evidence of our hypothesis that noise exposure is a factor in the Wisconsin data. There is much to learn about sampling procedures before we can extrapolate to the general population with complete confidence.

NON-NOISE EXPOSED SAMPLE

Much has been said and written about so-called presbycusis. Strictly defined presbycusis means hearing loss due to physiological changes with age. Any studies of hearing loss as a function of age are always confounded by the environment in which our ears operate. If we are to believe that occupational noise exposure produces an upward shift of the auditory threshold we must assume that the wear and tear of our non occupational noise exposures, such as transportation noises, audio communication, listening habits (hi-fidelity, televi-

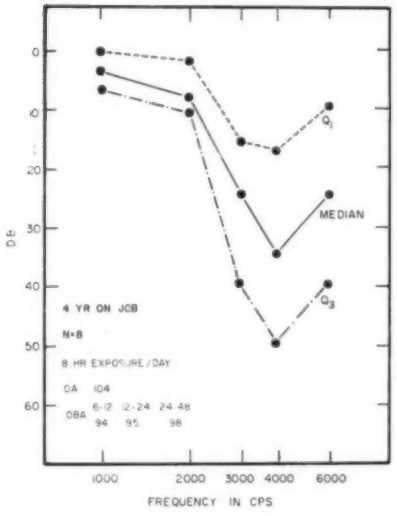

Figure 11

sion ,and radio) and a myriad of other noises we are continually bombarded with, will produce changes in addition to those that are physiological. In other words, before we can really determine the threshold changes found in presbycusis, we must measure hearing as a function of age in a population whose environment does not include the cacophony of modern civilization. Obtaining this kind of sample appears deceptively simple, but try as we might we have been unable to find a group that fits our criteria.

In lieu of such data, we present the following values obtained from a study of nearly two thousand professional and office type male employees. Each man was asked to record all activities that had been accompanied by noise enough to make it difficult to converse in a loud voice at arm's length. This included military service, sports, such as motor boating, hunting, etc. Figure 5 shows hearing level as a function of age in 328 men screened out of the two thousand originally examined. The only criteria used for screening were the

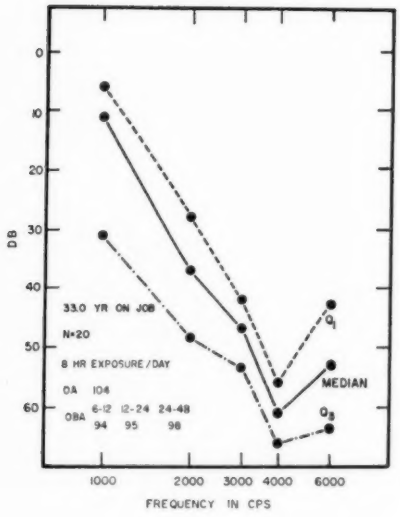

Figure 12

presence of or history of otological disease and a history of having been exposed to gun fire or noise levels high enough to make conversation difficult. When these data are compared with other similar data reported by various workers they show lower thresholds, that is, better hearing.

The first column in Figures 6 and 7 shows the same data distributed into centile groups at four age brackets, 20-29, 30-39, 40,49, 50-59 compared to two other population samples. The sample differences are now quite apparent. The median value (the fiftieth centile) at 1000 cps in the younger groups are practically the same in the three samples shown. Also, the distributions of the hearing levels by centiles at 1000 cps are very much the same in all the samples. Now the medians in the 20-29 year group at 4000 cps are almost the same but note the differences in the hearing level distributions particularly between the male "non-noise" exposed group and the "male general population" group. If our analysis had stopped with

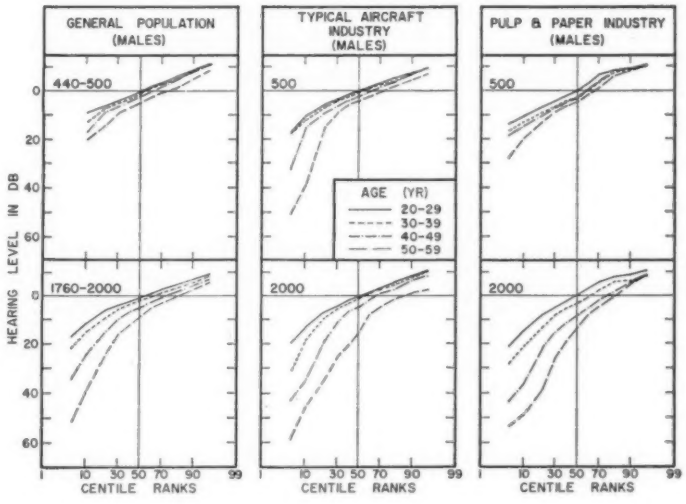

Figure 13

the median statistic we would have concluded that there is no difference between these samples. It is quite apparent that this is not true when the hearing levels are distributed according to centiles. In the "non-noise" exposed group 5% of the 50-59 year old subjects show a 60 db hearing level at 4000 cps whereas 20% of the general population 50-59 year old subjects show a 60 db level at the same frequency. Notice also the comparison with the female general population and the male general population. Each of these general population samples have an N of over 20,000. It is interesting to note that the female general population sample shows less hearing loss than the highly restricted "non-noise-occupation" male sample. Note the striking differences between the first two samples and the general male population. On the basis of such evidence we are convinced that hearing level data must be analyzed and displayed in this manner before subtle differences in samples will be demonstrated.

Figure 8 shows the data from a sample of males and females whose mean age is nine years. In this group 500, 1000, and 2000

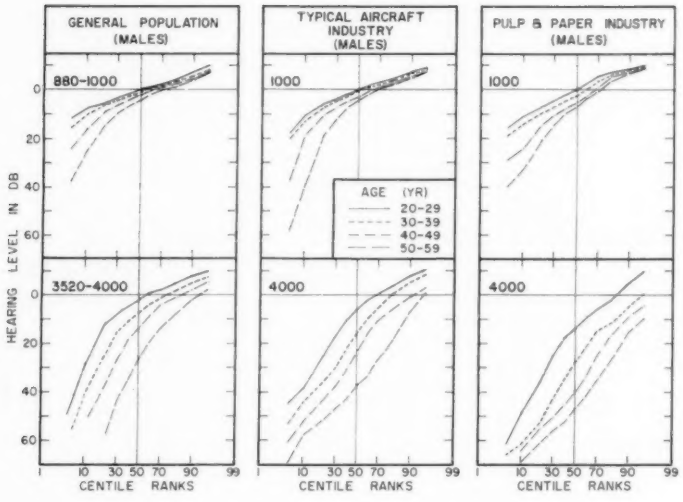

Figure 14

cps were so nearly the same they appear as a single solid line. The dashed line illustrates the data at 4000 cps. Notice how closely the male and female distributions resemble each other. The lower thresholds found in females, which are quite evident in adults, even young adults, are not shown by these data. The most logical explanation of this difference is that environmental factors which are quite different for adult males than for females has not shown its effect on these young children. We do not think it is illogical to assume that environmental noise is the reason for the difference in thresholds found in men and women. Other than the effect of aging, noise exposure is the only cause of hearing loss that affects the general population. One must certainly agree that otological disease either in childhood or adulthood is not enough more common in males than in females to explain the higher thresholds consistently found in men over 18 years of age. Experiments on temporary threshold shift as a function of sex show no difference in males and females. Both sexes shift equally when exposure is equal. If temporary threshold shift is an indicator of the effect of noise on hearing the evidence tends to show that males

are not more susceptible than females and that the higher thresholds seen in men are probably dependent on more exposure to noise. Further evidence of no sex difference in true presbycusis may be assumed by comparison with the eye. Presbyopia, which for all practical purposes is not related to environmental factors, is equal in men and in women of the same age. Obviously this question will not be answered properly until we can survey a population that has had none of the noise exposure found in our highly mechanized way of life.

NOISE EXPOSED SAMPLES

The effect of known noise exposure is well illustrated in Figures 9 and 10. A comparison of the male general population with two industrial samples shows striking differences as the noise level is increased. Both industrial groups have been exposed to continuous noise for eight hours a day. One group of 9653 men was exposed to an average of 84 db at 600-1200, 1200-2400, 2400-4800 cps. The other group of 338 men was exposed to an average of 94 db in the same bands. This average is commonly referred to as the speech interference level, abbreviated as SIL. The data are distributed in respect to age as indicated in the figures.

Figure 9 shows the comparisons at 500 and 2000 cps. At first glance the three groups look very similar at 500 cps. A closer look at the SIL 94 group shows a shift of the median and more hearing loss in all age groups. Because of sample size the 20-29 age group is omitted from the SIL 94 group. Again 2000 cps in the male general population and the SIL 84 group appear similar except for a general trend toward more hearing loss in latter sample. Note the striking difference in the SIL 94 sample, particularly in the 50-59 year age group. Figure 10 illustrates the data at 1000 and 4000 cps. The general similarity in the first two groups at 1000 cps is apparent. A close look, however, shows the same general trend toward more hearing loss in the SIL 84 group. In the SIL 94 group 1000 cps shows a marked difference. The data from the "SIL 94" group are particularly significant because of the hearing loss at 1000 and 2000 cps. These frequencies are of primary importance to hearing and understanding speech. Notice the changes in "SIL 84" and "SIL 94" at 4000 cps. At this frequency the influence of noise exposure is quite evident even in the "SIL 84" group. Note the very severe loss at 4000

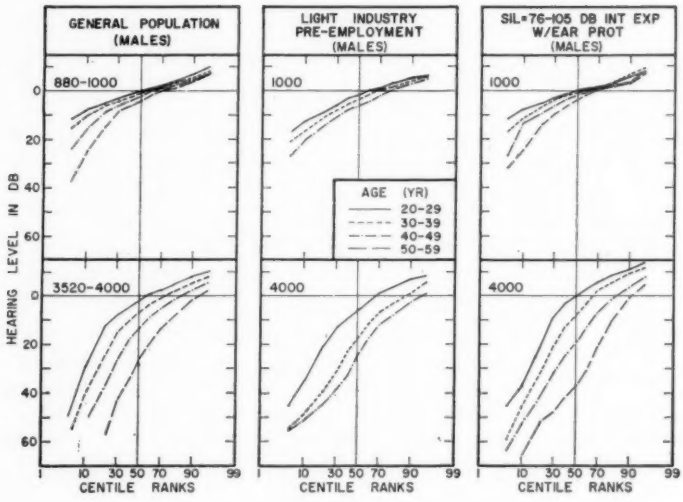

Figure 15

cps in the "SIL 94" group. Figures 11 and 12 show actual quartile audiograms on men who have been exposed to "SIL 94" for four years and 33 years, respectively.

There are several notable features in Figures 11 and 12 which merit attention. Notice the wide separation of the quartiles in Figure 11 as compared to the quartiles in Figure 12. It is apparent that when noise exposure continues long enough the tough ears eventually catch up to the tender ears. This catching up process probably indicates that there is a maximum shift that is a function of the exposure level. This maximum shift varies also with frequency. Four thousand cps nearly always shows the maximum change first and shifts more rapidly than the other frequencies, particularly those below 3000 cps. The 4000 cps shift seems to be almost universally true regardless of differences in the exposures common to industry. Figures 13 through 16 illustrate some of the subtle differences found in different types of industrial processes. Figures 13 and 14 show the general population group (N = 20,459) compared to 2018 aircraft factory employees,

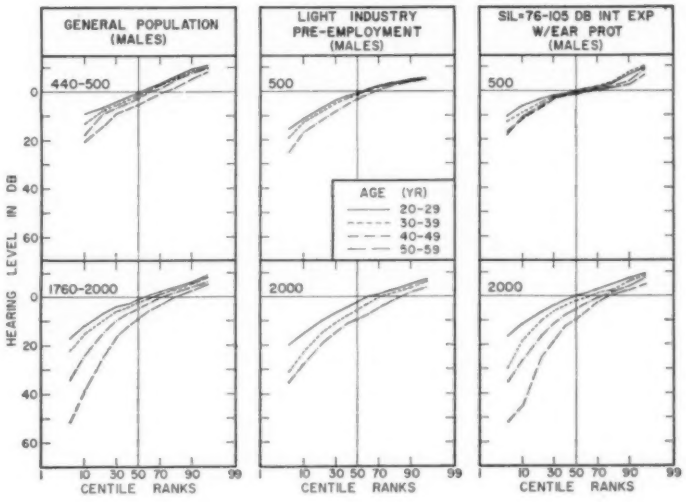

Figure 16

and 1596 pulp and paper manufacturing employees. Notice the apparent similarity of the three groups at 500 and 2000 cps. A close look reveals some slight differences, however. For example, more elevated hearing levels in the aircraft group at 500 cps in the older age brackets and slightly more elevated hearing levels at 2000 cps in the pulp and paper manufacturers. The differences between these industrial groups and the general population at these frequencies are slight and probably insignificant (Fig. 4). In contrast notice the differences at 1000 and 4000 cps. The aircraft factory employees show considerably higher levels at 1000 cps. Both industrial groups show higher levels at 4000 cps than found in the general population sample. The pulp and paper workers show higher levels at 4000 cps than those in the aircraft factory workers. Because of the wide differences in processes and the heterogeneity of the noise exposures in these industries, it is difficult to explain these relatively small differences in the distributions of these data. Figures 15 and 16 demonstrate a comparison between the same male general population data and 2395 pre-employment audiograms made by a large company whose processes

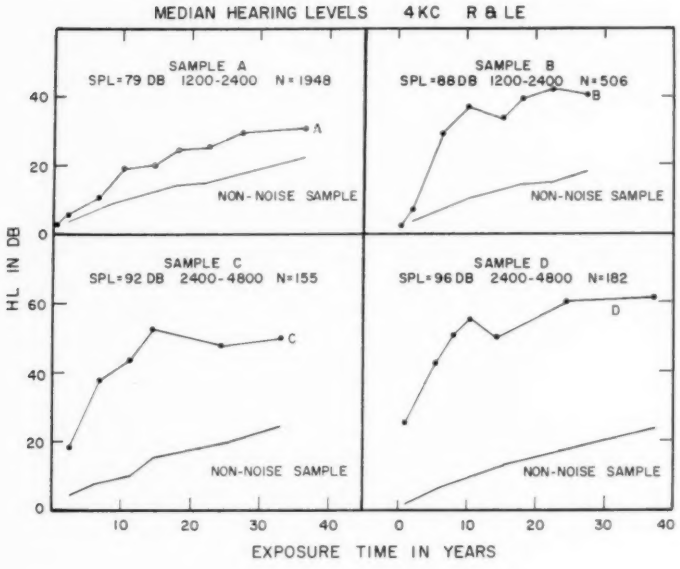

Figure 17

produces only moderate noise levels, and 1332 employees of a specialized developmental laboratory (Fig. 16). Notice the obvious similarity of these groups except at 4000 cps. This frequency shows an increased amount of hearing loss even in the pre-employments in the light industry sample.

COMMENT

There is much to be learned from these comparisons. It is obvious that noise exposure produces hearing loss but when noise-exposed samples are compared to the general population marked differences are evident only in the frequencies above 2000 cps in the samples whose exposures are continuous and above 85 db in the octave bands: 600-1200, 1200-2400, and 2400-4800 cps.

The difference between intermittent exposure and continuous exposure is quite evident when the "SIL 84" and "SIL 94" groups

are compared with the aircraft industry group. There are obvious differences between the aircraft workers and the SIL 84 group but striking differences are most evident when the SIL 94 group is compared to the aircraft industry sample.

The noise levels in these two samples are not the important parameter. The "SIL 94" group was exposed to 94 db continuously for 8 hours a day. The aircraft factory workers are exposed to levels that vary from 85 to 120 db but the exposure is intermittent during any work day and the group exposure duration is completely different for many reasons. Personnel turnover in aircraft plants is very high. Few persons work for more than two or three years at the same job and frequently even with the same company. Longitudinal studies are difficult under these conditions. Even when the employes stay with the same company they very seldom stay at the same job. Consequently it is next to impossible to describe noise exposure in these types of industries.

The "SIL 94" sample is taken from small highly specialized plants where only one product is manufactured. The plants are in small towns where personnel turnover is very low. They operate 24 hours a day and have done so for the past 40 years with no change in sound pressure level or spectral distribution since measurements have been possible.

In spite of the higher noise levels found in the aircraft industry the hearing levels are considerably lower in these employes. Actually the incidence of hearing loss is only slightly higher in these men than in the general population. Obviously the explanation must be the intermittency of the exposure.

In Figure 17 four samples are shown. The comparison is made between the median hearing levels as a function of years of noise exposure in each of the four samples A, B, C, D, and the median hearing levels of our so-called "non-noise" sample as a function of age. Each comparison is the same except for the change in noise levels as indicated. If the noise sample data are examined closely, four important facts emerge:

First, levels as low as 80 db produce more hearing loss than is found in a non-noise-exposed group (that is, non-industrial noise).

Second, as noise levels increase hearing levels increase. Notice the hearing level differences in respect to increase in noise level.

Third, most of the increase in hearing level occurs during the first ten years of exposure.

Fourth, the increase in hearing level occurring after ten years follows the same course as that found in the non-noise sample.

The lower curves in Figure 17, labeled non-noise sample, are taken from the data shown in Figure 5 which we have called "hearing loss as a function of age." If you will examine the shape of the upper curves in Figure 17 after the ten year point you will notice they closely resemble the shape of the lower curves. We believe that this is fairly conclusive evidence that on the average the maximum hearing loss due to noise exposure occurs in approximately ten years and that subsequent loss is related to aging. Such data can be very helpful in establishing prediction curves and standards for noise control. After we have obtained sample data from groups that have been exposed to various known levels and exposure periods we will be able to prepare prediction curves that can be used to estimate the hearing loss risk for various industrial operations. Further we will be better able to establish some of the relations of noise-induced hearing loss to age induced hearing loss.

CONCLUSIONS

1. Some method of equating audiometric data appears necessary before various samples can be compared with any semblance of validity. Threshold levels found in 17-19 years old males and females can be used as a common reference level.

2. If central tendency statistics only are used, subtle differences in audiometric data will be obscured. Distribution of the hearing levels into centiles will give much more information.

3. Before the effects of noise exposure on hearing can be established much more information about hearing loss in general and in non-noise-exposed populations is needed.

327 S. Alvarado St.

XLIII

TISSUE REACTION FOLLOWING RECONSTRUCTION OF THE OVAL WINDOW IN EXPERIMENTAL ANIMALS

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and

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In continuing our investigation of the tissue responses in experimental animals following specific and controlled trauma to the stapes and oval window, we have carried out three experiments which have revealed considerable information of interest to otologists at this time.

Recently, in human surgery, the oval window and stapes have been exposed to a variety of microsurgical procedures. Foreign substances designed to permit the transmission of vibrations and to simulate the normal action of the stapes have been substituted in the middle ear to replace the footplate and the crura. In many instances after crurectomy, the break in the conductive mechanism between the incus and the footplate of the stapes has been bridged by a prosthesis of plastic tubing or metal. The footplate of the stapes itself has been removed and the oval window covered by homografts of fascia, buccal mucosa, vein or fat. It is rarely possible to examine under the microscope the tissue responses to these transplanted substances in man. Occasionally a biopsy is taken at a secondary operation but the degree of hearing improvement, or the lack of it, is usually the only indication of how well these grafts and foreign substances are being accepted by the human ear. Consequently we have organized a series of experi-

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From the Otology Research Laboratory of the Manhattan Eye, Ear and Throat Hospital, New York, N. Y.

This investigation was aided by grants from the American Otological Society and from the Department of Health, Education and Welfare, National Institute of Health.

Fig. 1.—A membrane forms across the oval window after the footplate has been removed or partially removed. Here the posterior stapediovestibular articulation is intact in both cases. Postoperative time 5 months and 7 months, respectively. Cat No. 12 Aut. No. 175-140; Cat No. 25 Aut. No. 295-141 Lft.

ments in laboratory animals in which these responses could be studied in detail in order to obtain information which would give some encouragement or warning regarding the use of similar techniques in man.

Again we must concede that tissue responses in animals cannot be considered to be the same as those which occur in man. However, basic tissue reactions have some similarity in all mammals and may be relatively significant.

We have shown in a previous publication[1] that the oval window following stapedectomy is closed quickly by a membrane derived from the endosteum and the periosteum of the oval window (Fig. 1). We have reason to believe, however, that this rapid tissue response does not occur in some cases, leaving an open oval window with a leak of perilymph. This may account for an occasional dead labyrinth following mobilization of the stapes in man even though the structures of the inner ear were not traumatized. These cases are few in number and we are grateful for nature's kindness in providing such an active tissue response which protects the inner ear. Consequently, covering the oval window with some substance was believed to be important as it would insure a rapid sealing of the labyrinth. Although several substances have been used to cover the oval window following stapedectomy, a study was made of the tissue reactions to autogenous grafts of vein and compressed pledgets of Gelfoam. In these experiments the stapedes were removed and the oval window niche was denuded of its mucoperiosteum. A vein taken from the hind leg of the same animal was used to cover the fenestra. A piece of polyethylene tubing or Gelfoam was placed over it and under the lenticular process of the incus. The animals were allowed to live various lengths of time and when sacrificed the tissue responses to this surgery were studied in detail. Thus, we have had an opportunity to observe the tolerance to polyethylene tubing when implanted in the middle ear. We have obtained an impression regarding the fate of the vein graft and its influence on the labyrinth. In some respects these tissue responses were found to be encouraging and other findings permit some serious thinking regarding the continued use of the vein as a substance suitable for closing the oval window.

The common use of Gelfoam in the middle ear and at the oval window prompted a study of the tissue reaction to this foreign sub-

Fig. 2.—Some serious reactions have occurred following the use of the vein graft with polyethylene strut. Ears from three different cats are shown. Cat *A* lived 5 months postoperatively; Cat *B*, 5 weeks; Cat *C*, 6 months. Results in *A* appear successful at this level. See Figures 3 and 4, however, for other levels. In Cat *B* aseptic fibrosis has completely obliterated cochlea and vestibule. In Cat *C* the fibrosis has been replaced by newly formed bone and fatty marrow. Even the spiral ganglion cells are markedly reduced in number.

stance. In these experiments it was used to close the oval window after the stapes was completely removed. In other animals the Gelfoam pledget was placed over the fragmented footplate of stapes which was allowed to remain *in situ*.

In the third experiment a different type of reconstruction was attempted. The stapes was removed from the middle ear of one animal and inserted in position at the oval window of another. This was done with the least possible trauma. The oval window niche of the recipient animal was not traumatized and the transplanted stapes remained intact. By this means we could be sure that the blood supply and ligamentous attachments were completely severed leaving the transplanted stapes without its normal channels of nutrition. This experiment was inspired by our belief that often the crura of the stapes have been fractured during the mobilization procedure in man and at times the blood supply may have been severely compromised.

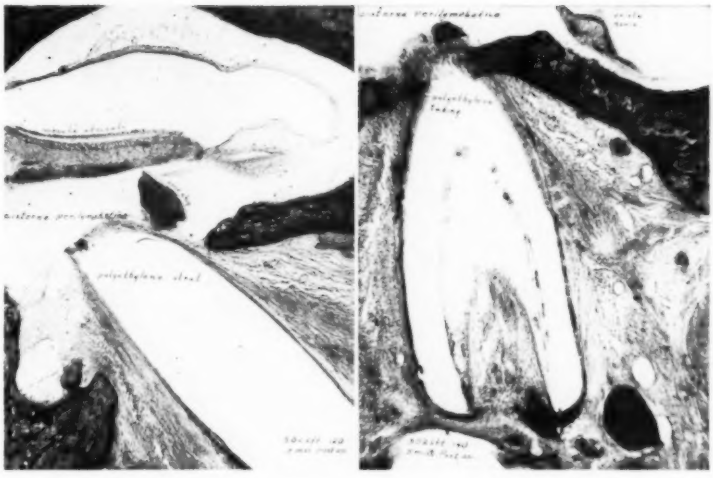

Fig. 3.—At these levels it is clear that specimen 302 contains bone fragments thrust within the labyrinth. These have damaged the labyrinth slightly and have instigated fibrosis in the perilabyrinthine spaces.

Regardless of this, these stapedes apparently survived in the middle ear. Our results in these animals reveal some facts which may be pertinent in the survival of this ossicle when the blood supply was totally disrupted.

In other animals the stapes was interchanged with another of the same litter or with a stapes which had been stored in a bone bank for a considerable length of time under refrigeration. The implication of this experiment is clear. Can the stapes be stored for this type of transplantation as is the case with other bones used in orthopedic and plastic surgery?

In two other animals after the stapes was removed the incus (one homologous, one heterologous) was used to cover the oval window. Our observations have been interesting and reveal useful information regarding the viability of the transplanted ossicles and the tissue reactions following their use in the reconstruction of the oval window.

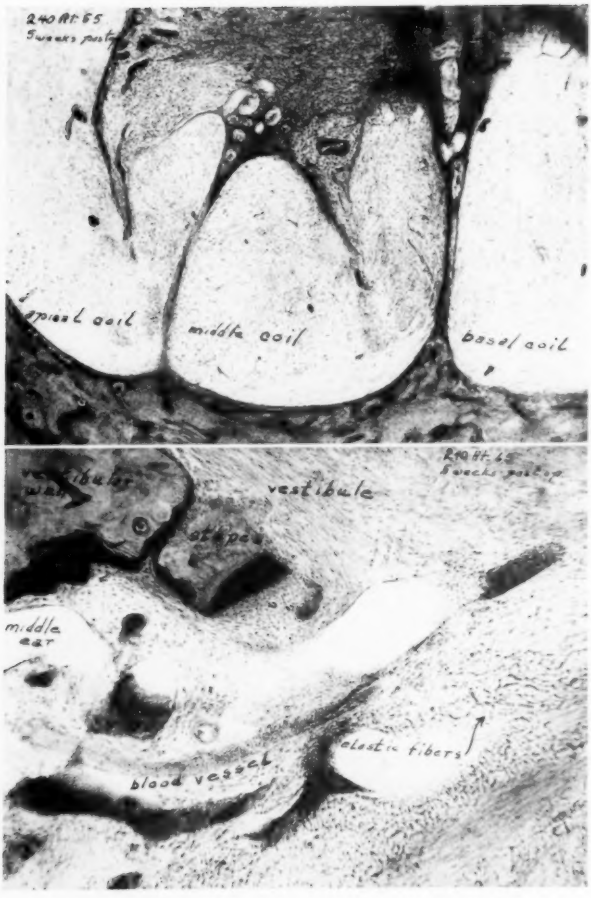

Fig. 4.—(*Upper photo*) Complete obliteration of cochlear spaces and organ of Corti, 5 weeks after application of vein graft and polyethylene strut. Spiral ganglion cells are present but vacuolated and overwhelmed by enlarged satellite cells. No. 240-55. (*Lower photo*) Detail of oval window where vein was placed. Lower right center field shows scattered elastic fibers, only evidence of the vein's presence. Congested vessels cross the window. A fragment of stapes is ankylosed to anterior vestibular wall.

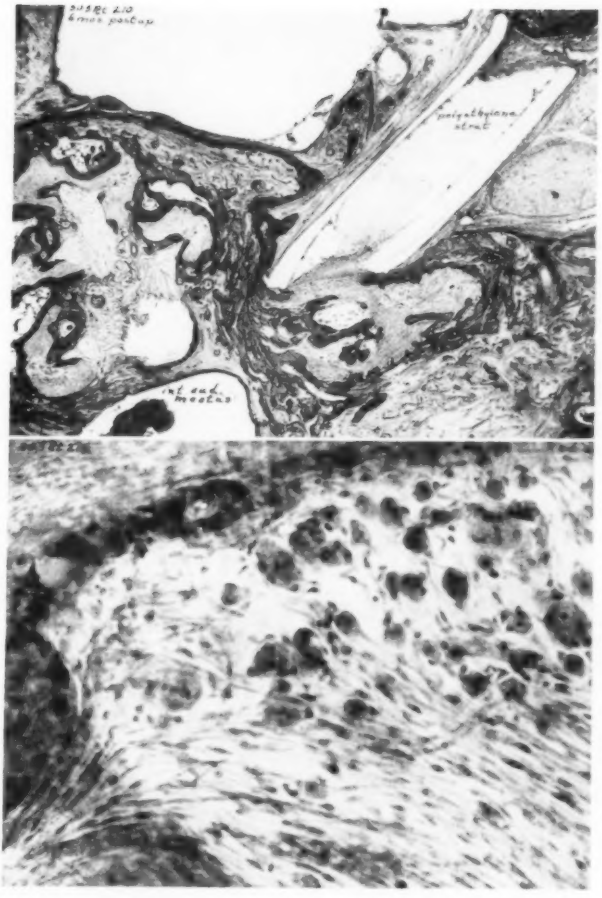

Fig. 5.—Higher magnification of modiolus of Cat *C* showing scattered remnants of spiral ganglion (*upper photo*). No. 303 Rt. 210. Detail of spiral ganglion cells showing scattered location, bizarre shapes and disparate sizes of neurones. 6 mos. postoperative.

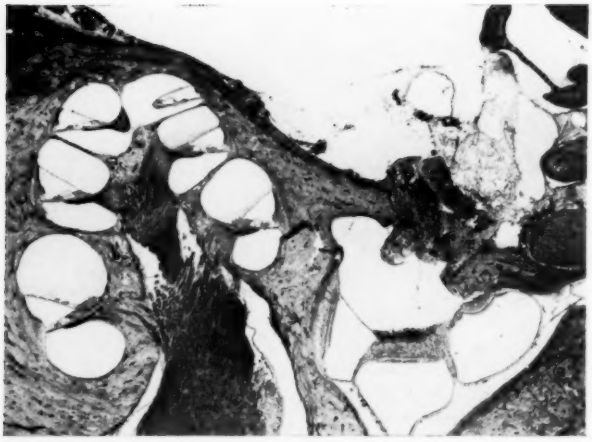

Fig. 6.—No. 340 right, sec. 80. Postop. time, 3 days. Vein plug held in place by gelfoam. The vein has become attached to vestibular wall. Reissner's membrane is in situ throughout but has a slight break in the basal turn. Here also the sulcus cells are ripped from basilar membrane. Deiter's cells and Hensen's cells are missing. At higher levels the organ of Corti is in good condition.

The results of our experiments will be reported in three parts:

Part I. Reconstruction of the Oval Window with Vein Graft.

Part II. Reconstruction of Oval Window with Gelfoam.

Part III. Reconstruction of Oval Window with Transplanted Stapes, Homologous, Heterologous and Banked Ossicles.

Today we shall present Part I and Part II.

EXPERIMENT I. VEIN GRAFT

Procedure 1. Placement of vein graft over an oval window from which the stapes had been completely removed; endothelium of vein facing middle ear; polyethylene strut supporting vein. Cat No. 22,

Aut. 302, left, 5 mos.; Cat No. 25, Aut. 295, right, 4 mos.; Cat No. 26, Aut. 303, right, 6 mos.; Cat No. 27, Aut. 247, right, 1 mo., 10 days; Cat No. 29, Aut. 240, right, 1 mo., 6 days.

Procedure 2. Placement of vein graft ("plug") over an oval window from which the stapes had been completely removed; endothelium facing middle ear; vein held in place by Gelfoam (1 ear). Cat No. 39, Aut. 340, right, 3 days.

Procedure 3a. Placement of vein graft over oval window from which stapes had been partially removed; vein held in place by Gelfoam; endothelium facing middle ear. Cat No. 36, Aut. 354, right, 10 days.

Procedure 3b. Placement of vein graft over oval window from which stapes had been partially removed; endothelium of vein turned inward toward inner ear; vein held in place by Gelfoam. (1 ear). Cat No. 41, Aut. 364, left, 13 days.

MICROSCOPIC OBSERVATIONS

Experiment I

Procedure 1. When polyethylene tubing is placed over a vein graft and engaged with the lenticular process, it apparently maintains this position fairly constantly. (It should be mentioned at this point that these cats are not constantly confined in their cages but are taken out for exercise and observation following recovery.)

Certain hazards seem to accompany the vein and polyethylene tubing procedure. Figure 2 demonstrates in series, vein grafts placed over the oval window of cats permitted to live for varying lengths of time postoperatively (5 months, 5 weeks and 6 months respectively). In photo A (302 left) the position of the strut is evidenced as a clear arch extending somewhat beyond the level of the oval window, into the cisterna perilymphatica where a portion of the stapedial footplate dangles beside the tubing. At this level no apparent damage has been done to macula utriculi nor macula sacculi. Cochlea is relatively normal with distortion in position, however, of Reissner's membrane, in the upper middle coil. In the basal coil, Hensen's cells are distorted in shape. Furthermore a band of fibrous tissue extends

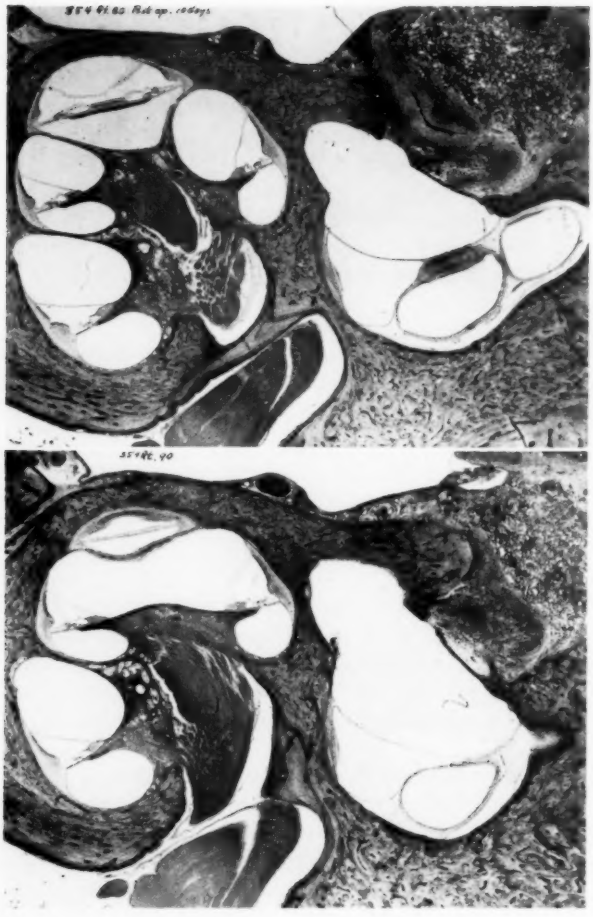

Fig. 7.—Cat, Aut. No. 354 right, sec. 80 and 90. Postoperative time, 10 days. Partially denuded oval window, over which has been placed a vein graft held in situ by gelfoam. Extensive fibrosis surrounds these structures but there is no invasion of the inner ear. There is, however, disruption of outer and inner sulcus cells, Hensen's cells and Deiter's cells.

Fig. 8.—Vein graft with endothelium turned toward inner ear, placed over oval window from which stapes had been partially removed. Vein held in place by gelfoam. Mucosa stripped. This yielded an excellent organ of Corti. Time postoperative, 13 days. Cat No. 41, Aut. 364 left, section 80.

across the anterior part of the cisterna perilymphatica. There is no otitis media and no labyrinthitis. Apparently the head of the autogenous stapes was inadvertently left resting on the vestibular wall. Its presence has caused no untoward reaction. In Figure 3, high powers taken at higher levels, we note fragments of bone within the labyrinth and slight injury to the lateral wall of the horizontal semicircular canal has occurred. This cat was sacrificed 5 months postoperatively. At the time of sacrifice the cat was playful and seemed to respond to sound but could not be induced to stand up on its hind legs in play. The opposite ear which had a stapedial transfer was in excellent condition except for ankylosis of the anterior part of the footplate.

Let us now examine the illustration in photo B of Figure 2. We can readily identify cochlea, vestibule and the position of the strut of polyethylene tubing. No fragments of stapes or bone chips can be seen at any level. We see that the middle ear is free of infection but the spaces of the inner ear, both cochlear and vestibular, are solidly

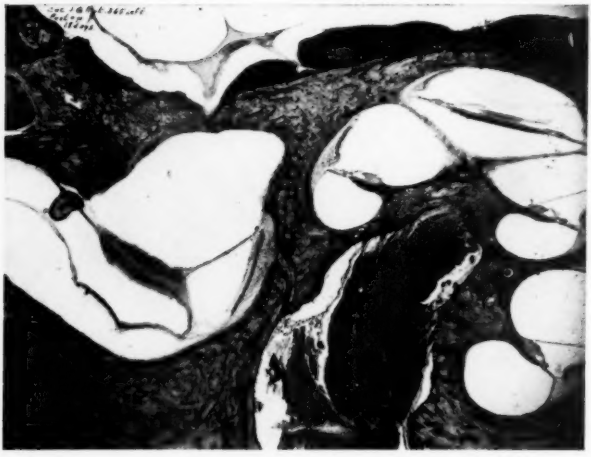

Fig. 9.—Gelfoam only was placed over an oval window from which the stapes had been completely removed. The gelfoam has maintained its location in the oval window but not because of any well-defined membrane. Lysis of the gelfoam is beginning. Organ of Corti in basal turn shows liquefaction of specific cells. Cat No. 38, Aut. No. 365 left, section 80. Postoperative time, 13 days.

filled with fibrous tissue. There are no abscesses in evidence in the inner ear at any level in the serial sections of this specimen. No polymorphonuclear cells are present in the blood within the blood vessels. This fibrosis is therefore an aseptic process. It has extended throughout the labyrinth from the superior semicircular canal to the inferior and horizontal. No end-organs are maintained. The upper photo of Figure 4 shows the dissolution and fibrotic replacement of the bony spiral lamina. The cochlear coils are filled entirely with whorls of fibrous tissue which have destroyed organ of Corti, basilar membrane and spiral ligament. Pathological changes in the ganglion cells are also present. Satellite cells are larger than normal and no longer maintain their proper position encircling each ganglion cell but spread diffusely throughout the area as in gliosis. The ganglion cells are reduced in size, showing vacuolization of cytoplasm. In the basal turn of the cochlea, bone is beginning to be deposited in the perilymphatic spaces. At the oval window, as demonstrated in the lower

photo of Figure 4, lie the only remnants of the vein graft. A few elastic fibers are seen here engulfed in the overwhelming fibrotic reaction. This specimen was just 5 weeks postoperative.

Illustration C of Figure 2 presents Cat No. 26, Aut. No. 303, right, section 190. A vein graft was inserted over the oval window and held in place by polyethylene tubing as in the previous specimen. The tubing is still engaged with the lenticular process of the incus, 6 months after the operation. Middle ear is essentially free of infection. Nevertheless, the whole inner ear is completely filled with fibrous tissue and new bone formation, bone predominating. Even fatty marrow spaces are forming in some of the cochlear coils. Destruction of the organ of Corti and vestibular end-organs, as in the previous case, is complete. Marked atrophy of the spiral ganglion exists throughout. A few cells in the modiolus remain viable and exhibit the greatest disparity in size, some of them being one and two thirds times the normal size. For details of these ganglion cells and the tissue reaction at the oval window see Figure 5.

Of the six ears processed using the vein graft and polyethylene tubing only one shows a good result. This one has a good organ of Corti after 5 months but since there is fibrosis within the cisterna we cannot say what might happen eventually. One ear developed labyrinthitis. The others showed aseptic fibrosis and new bone formation completely destroying end-organs and spiral ganglion cells. Vestibular ganglion cells were still intact but the protoplasm appeared abnormally granular and the nuclei contained more pronounced chromatin bodies than normal.

Experiment I

Procedure 2. In the second part of Experiment I, a vein plug was held in place over the stapedectomized oval window by Gelfoam (No. 340, right ear, sec. 80). The result is illustrated in Figure 6. The mass of Gelfoam employed in this case was relatively small. Three days after this operation the cat died from peritonitis due to a ruptured intestinal wall. There was no meningitis, no pleurisy nor lung involvement.

The microscopic examination of the ear reveals that the vein is already attached to the vestibular wall at least in some regions. With-

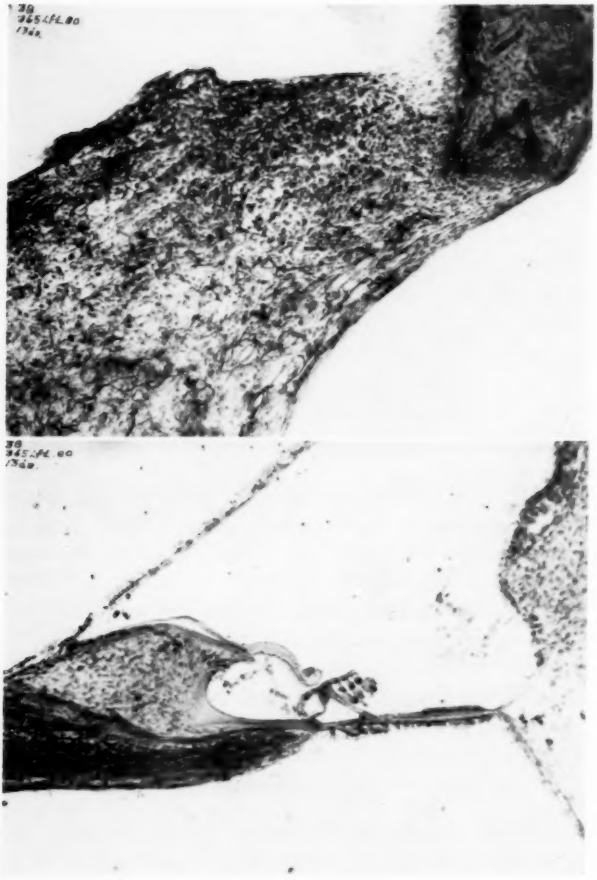

Fig. 10A.—Detail showing gelfoam attached to bony wall of oval window and well-contained therein. Lysis of the gelfoam is beginning, however, in the lower left field. Cat No. 38, Aut. 365 left. Postop. time, 13 days. 10B.—Detail showing autolysis of external and internal sulcus cells, Hensen's cells and Deiter's cells. The three outer hair cells hang suspended from the cuticular border. Basal turn of above specimen.

in these three days no untoward fibrotic reaction has occurred around the Gelfoam in the middle ear. Organ of Corti is fair, post mortem changes accounting for some of the pathology. In the cochlea it is apparent that free blood is in the scala vestibuli. Sulcus cells, both external and internal are completely stripped from basilar membrane in the basal coil of the cochlea. Nuclei of Deiter's cells lie abnormally high in their cells, Nuel's space is no longer clearly differentiated and there is a tendency for Hensen's cells to fuse and lack nuclei. Mucosa was stripped from promontory with no bizarre fibrosis resulting.

Experiment I

Procedure 3. A vein graft was placed over an oval window from which the stapes was not completely removed, four fifths of the length of the stapes remaining in situ. This procedure involved two different cats and two ears. It may be significant that the result in the inner ear is described as good and excellent, respectively for these two cases. Figure 7 illustrates Cat No. 354, right sections 80 and 90. Unfortunately the postoperative time is only 10 days. Here also there is marked edema and displacement of outer and inner sulcus cells.

The upper photo in Figure 7 shows the endothelial lining of the vein infolded upon itself, as a double layer. It presents a cuboidal type of cell as described by Myers.[2] This is not evident in the lower photo but it is clear that the vein is enveloped in fibrotic tissue which is attached to the bony wall of the oval window. Beyond this fibrosis lies the large mass of Gelfoam. Within the interstices of Gelfoam red blood cells may be seen as well as early large fibroblasts. Lateral to the Gelfoam more fibrous tissue is found. No otitis media is present.

The second case in this group is illustrated in Figure 8. The procedure in this case was like the preceding, with one exception, the endothelial lining of the vein was turned toward the inner ear, deliberately. This was in Cat No. 41, Aut. 364, left ear. In the microscopic sections the endothelial lining can no longer be identified as such but there is very definitely a membrane crossing the oval window medial to the densely fibrous vein wall. Lateral to this the interstices of the Gelfoam can readily be recognized. They are filled with pus cells as there is a very heavy otitis media. In spite of this, there is no

Fig. 11.—Gelfoam placed directly over stapedectomized oval window and held in place by polyethylene tubing. The gelfoam tends to undergo lysis and to fragment into vestibule. This has caused no tissue reaction but a toxic lysis of sulcus cells, Hensen's cells and Deiter's cells in the basal coil occurred. Cat No. 38, Aut. No. 365, 120 and 130 right. Postop., 2 mos. 6 days.

invasion of the inner ear. Of the 26 ears processed in this experiment, this is the most perfect organ of Corti and sulcus cells we possess, this in spite of the fact that the supporting perilymphatic connective tissue trabeculae of the vestibular labyrinth are completely missing. Furthermore we definitely stated that we had failed to get good perfusion in this case. The postoperative time was 13 days.

EXPERIMENT II. GELFOAM WITHOUT VEIN

Procedure 1. Stapes completely removed; Gelfoam placed over oval window. Cat No. 38, Aut. 365, left, 13 days.

Procedure 2. Stapes completely removed; Gelfoam placed over oval window and held in place by polyethylene tubing. Cat No. 36, Aut. 354, left, 2 mos.; Cat No. 37, Aut. 370, right, 2 mos., 3 wks.; Cat No. 37, Aut. 370, left, 2 mos.; Cat No. 38, Aut. 365, right, 2 mos., 6 days.

Procedure 3. Gelfoam and polyethylene tubing were placed over an oval window in which part of the stapes or a multiple-fracture footplate was left in situ. Cat No. 35, Aut. 366, right, 25 days. Cat No. 41, Aut. 364, right, 2 mos., 6 days.

EXPERIMENT II. GELFOAM WITHOUT VEIN

Procedure 1. Gelfoam only was placed over an oval window from which the stapes had been completely removed. This was done in one ear only, Cat No. 38, Aut. 365, left. The result is illustrated in Figure 9, section 75. In spite of the presence of some infection in the middle ear the Gelfoam has remained in situ and properly positioned across the fenestra although no well defined membrane can be seen (Fig. 10a). Inner ear is clear. There is damage to the outer and inner sulcus cells, Hensen's cells and Deiter's cells. However, the three outer hair cells hang suspended from the cuticular border, unsupported by the Deiter's cells (Fig. 10b).

Procedure 2. Gelfoam and polyethylene tubing were placed over oval window from which the stapes had been completely removed in this procedure. Figure 11 illustrates two levels from a cat's ear in which Gelfoam was placed directly over the stapedectomized oval window and held in place by polyethylene tubing. It is apparent that

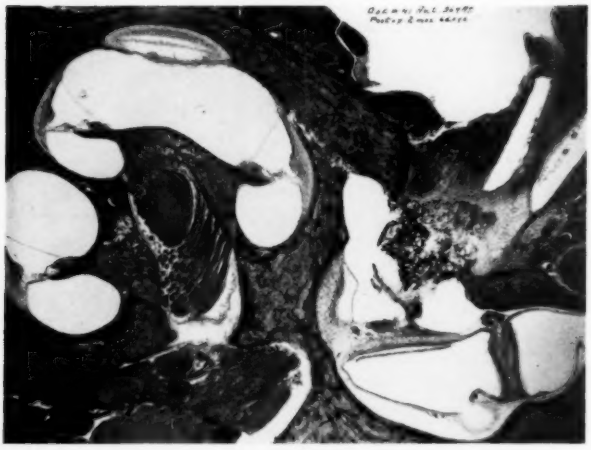

Fig. 13.—Part of footplate removed. Gelfoam applied over oval window and held in place with polyethylene tubing. The fragmented stapes has fallen within vestibule and is poised at base of macula utriculi where early fibrosis occurred. Particles of lysed gelfoam also enter vestibule. Organ of Corti and basilar membrane show lysis. Cat No. 41, Aut. No. 364 rt. 100. Postop. time, 2 mos. 6 days.

particles of Gelfoam are falling within the vestibule. No fibrosis or other cellular growth has been incited by their presence. They seem to flake off from the main mass by a process of lysis within the Gelfoam. The presence of autolytic changes in the organ of Corti of the basal turn may be signficant and may be related to the lysis of the Gelfoam itself. This specimen is 2 months and 6 days postoperative. At the time of sacrifice this cat was in excellent condition and was crying loudly for food.

Figure 12 is a photographic demonstration from two levels of a temporal bone from a cat subjected to the same procedure as the preceding specimen. But in this case a heavy otitis media developed. The polyethylene strut failed to remain in position. It lies at a higher level, not photographed. The endolymphatic system of the inner ear has not been invaded by the purulent disease process as yet but lytic changes are present. Perilymphatic system is extensively replaced by

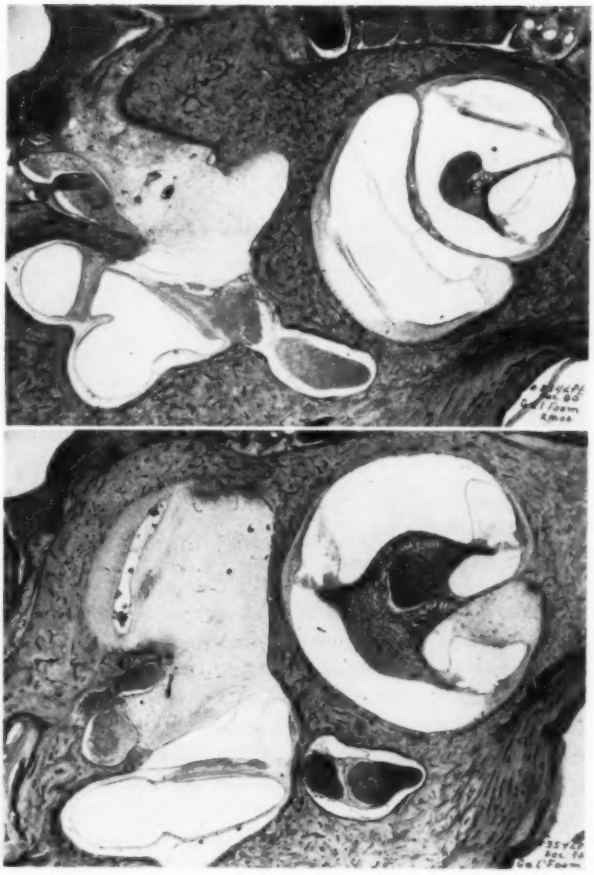

Fig. 12.—Gelfoam placed over window after stapedectomy. No surgical damage has occurred to crista, macula utriculi nor outer wall of saccule. But gelfoam has entered scala vestibuli as seen in lower photo. It is surrounded by dense fibrous tissue, extending into scala vestibuli of middle coil. New bone is beginning to appear in the basal coil. Fibrous tissue in oval window displaced the tubing superiorly and was not photographed. A lymphadenitis is now present but does not yet involve the inner ear. No. 354 left. 2 mos.

Fig. 14.—Gelfoam placed over a partially removed stapes and held in situ by polyethylene tubing. Note the foreign body giant cells along the inner contour of the tubing. The footplate is slightly subluxated and the gelfoam is undergoing lysis. A second piece of tubing lies in middle ear. A fulminating otitis media is present. Cat No. 35, Aut. 366 rt. Postop. time, 2½ months.

fibrous tissue, extending to the middle cochlear coil. As shown in the lower photograph, particles of Gelfoam lie within the scala vestibuli of the basal cochlear turn, completely surrounded by fibrous tissue. New bone is beginning to form near the vestibular wall. The animal, Cat No. 36, Aut. 354, left, was sacrificed 2 months postoperatively.

Specimen 37, Aut. 370 was exposed to the same procedure of complete removal of stapes. Ears were obtained 3 months and 2 months, 3 weeks postoperatively. Both ears showed fibrosis and new bone formation with a paradox. In one the cochlea was primarily involved, in the other, the vestibule. This cannot be explained on the basis of any known difference in procedure.

Procedure 3. Gelfoam and polyethylene tubing were placed in the oval window. The footplate had intentionally not been completely removed in these specimens. As shown in Figure 12 the

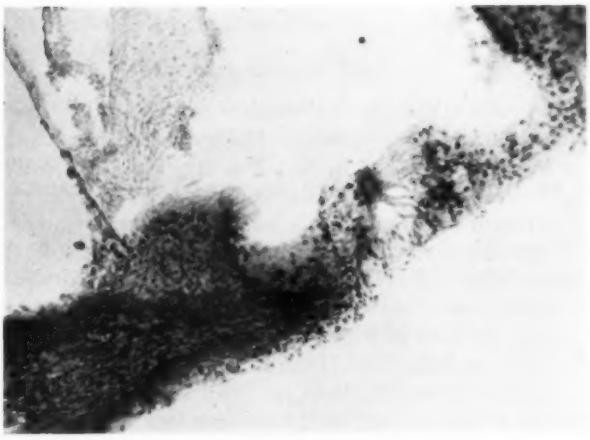

Fig. 15.—Autolysis may occur in the scala media in specimens directly exposed to the gelfoam over the inner ear. Here tectorium is sloughed from limbus and slight evidence of basilar membrane exists. Cat No. 36, Aut. 354 left. Postop. time, 2 months.

polyethylene strut has remained in position but the Gelfoam is undergoing lysis and is slipping into the cisterna perilymphatica. The posterior half of the stapes has also fallen into the inner ear and is poised at the base of the macula utriculi where slight fibrosis is present. Slightly more fibrosis has occurred on its lateral surface, attaching it to the mass of Gelfoam. Lytic changes have again occurred in the cochlea even to the extent of causing the disappearance of the basilar membrane itself although the cells of the organ of Corti are still present. A heavy otitis media is present but the purulence has not invaded the inner ear. The postoperative time is 2 months and 6 days. A similar condition exists in Cat No. 35, Aut. 366, except that the stapes has remained in situ and is showing early signs of regenerating bone[3] (section 70, two and one-half months after operation). The condition is illustrated in Figure 14. Observe that an extra piece of tubing lies in the middle ear.

There is a tendency for liquefaction of the organ of Corti in the specimens where Gelfoam came in contact with the inner ear. Figure

15 from Cat No. 36, Aut. 354, left, shows dissolution of tectorium and basilar membrane itself.

SUMMARY AND CONCLUSIONS

Nine ears in which the oval window was covered by a vein graft have been studied microscopically. In six of these polyethylene tubing was inserted into the middle ear along with the vein graft, as previously described. It is evident that the polyethylene strut remained as placed fairly constantly between the oval window and the lenticular process of the incus, surrounded by fibrous tissue. Although there was relatively little tissue reaction to the polyethylene tubing in these experiments considerable reaction followed the use of the vein. In five of the six cases in which the vein was applied to the oval window with the endothelial surface facing the middle ear, an active fibrotic reaction occurred within the inner ear. In most animals the reaction was severely damaging to cochlear and vestibular structures. Although some evidence of infection was present in the middle ear of three cases, in three this reaction was a completely aseptic process. We are able to conclude, therefore, that this overwhelming fibrotic response within the cochlea was not on an infectious basis.

In one animal in which the cochlea was found to be in good condition, four-fifths of the stapedial footplate remained in situ and the vein graft was applied over it. One other animal was found to have an excellent cochlea. Here the vein was applied over the oval window as in the above case but with the endothelial surface toward the inner ear. Although both animals were sacrificed within two weeks it may be that the fragments of the footplate were protective in both instances.

The vein graft also stimulated an extensive fibrotic reaction in the middle ear whenever used. After a period of time the vein could not be recognized as such since it was completely engulfed in the fibrotic reaction. The fibrosis, except in the cases just mentioned, was not confined to the middle ear but invaded the cochlea destroying to a greater or lesser extent, the sensory structures therein. This process continued in some specimens even to new bone formation.

Gelfoam was placed over the oval window in eight cases, four of these contained fragments of stapes footplate in the oval window.

The similar extensive fibrotic tissue response which followed the use of the vein graft occurred in three of the eight cases. In all of these three the footplate was completely removed leaving an unprotected oval window.

In general, fibrosis in response to the Gelfoam was found to be considerably less extensive. Again, when fragments of the footplate were allowed to partially protect the oval window, fibrotic reaction within the cochlea occurred less frequently.

An unexplained reaction was observed in two specimens in which the Gelfoam was used directly over the unprotected oval window. In these the basilar membrane could no longer be identified and in the basal coil Deiter's cells were missing as well as Hensen's and sulcus cells. The etiology of this damage may be of chemical toxic nature.

On the basis of these findings the tissue responses to the vein and to Gelfoam have revealed the existence of certain deleterious effects on the inner ear when these substances are used in the reconstruction of the oval window. When a considerable portion of the footplate was allowed to remain in situ to protect the inner ear these surgical techniques were less damaging to the cochlea.

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XLIV

THE MANAGEMENT OF MIDDLE EAR LESIONS SIMULATING OTOSCLEROSIS

FRANCIS A. SOOY, M.D.

SAN FRANCISCO, CALIF.

A significant number of patients with conductive hearing loss and intact tympanic membranes will be found at the time of surgical exploration to have some condition other than otosclerosis.

In reviewing our series of 1112 operative procedures (233 fenestrations and 879 stapes) involving 865 people covering a period of twelve years, we have found 37 patients who fall into this category for a total of 4.2%.

In some instances the correct diagnosis was made before surgery; in others it was not suspected.

Many of the surgical procedures used would not be employed today, but it is hoped that our experiences will be helpful to others in this field.

These cases have been divided for convenience into four groups:

1. Defects of the incus	1.0%
2. Post-inflammatory middle ear diseases	1.9%
3. Non-otosclerotic stapes ankylosis	0.4%
4. Congenital anomalies	0.9%

In the interest of clarity hearing levels will be expressed as equivalent speech reception thresholds in the average of the two best pure-tone thresholds at 500, 1000, and 2000 cycles. These levels are in close

From the Division of Otolaryngology, University of California Medical School, San Francisco 22.

agreement with the actual speech reception thresholds. All audiometry including that done in surgery was carried out by audiologists from the University of California Audiology and Speech Clinic.

1. DEFECTS OF THE INCUS

Nine cases of discontinuity of the incudo-stapedial articulation were divided etiologically as follows:

A. Necrosis of the long process	4 patients
B. Atrophy of the long process leaving a thin fibrous connection	3 patients
C. Trauma	2 patients, 3 ears

Two patients had concomitant otosclerosis, one in the same and one in the opposite ear. An additional case with a history of prior stapes surgery was found to have destruction of the lenticular process and anterior crus. This case it was felt should be excluded. Seven patients had a bilateral hearing loss, two a unilateral loss.

There was a definite history of infection in all patients showing necrosis of the incus and some tympanic scarring was also present in each instance.

Two patients with atrophy of the long process of the incus (Fig. 2) had prior ear infection with scarred eardrums, and onset of hearing difficulty during adult life. One, a boy of nine, showed no evidence of scarring, had been hard of hearing since birth, and had an ossicular anomaly in the opposite ear suggesting a congenital defect.

Two cases of traumatic discontinuity were encountered, one due to accidental surgical removal of the incus bilaterally (Fig. 3) following mastoid surgery, and one instance of posterior disruption of the incudo-stapedial joint of obscure etiology (Fig. 4). Only two out of the nine showed a unilateral hearing loss.

Surgical Management. Figure 1 summarizes the method used. Two cases were treated by fenestration of the horizontal canal. One obtained useful hearing, one gained 22 decibels, but was far short of useful hearing, one case refused surgery. The remaining six ears were treated as follows:

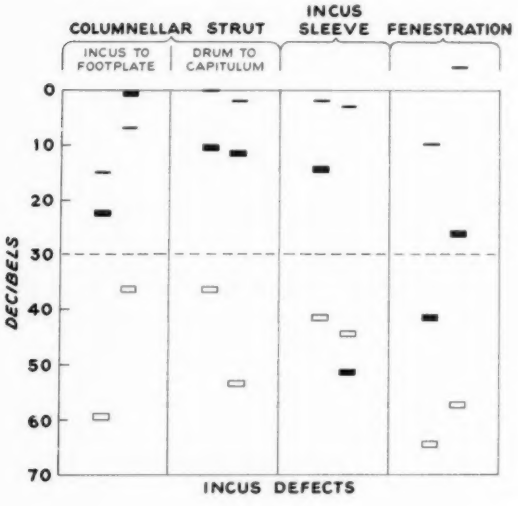

Figure 1

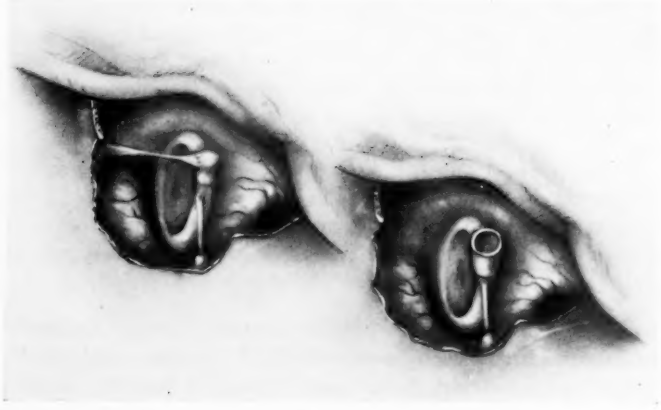

Figure 2

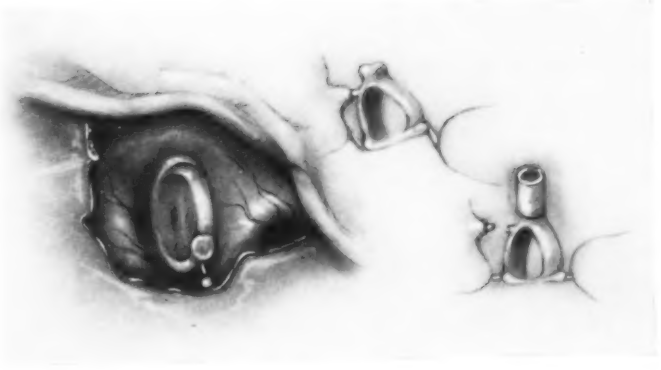

Figure 3

Figure 4

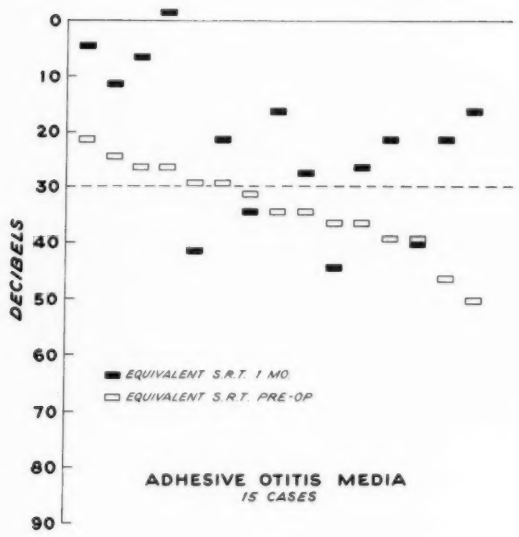

Figure 5

Incus Sleeve. Where there was sufficient long process remaining, a piece of 90 polyethylene tubing was slipped over this process, and after fashioning an appropriate diamond shaped hole, snapped on the capitulum of the stapes (Fig. 6).

RESULTS:	*Gain (loss)*	*Residual Bone-Air Gap*
1.	28 decibels	13 decibels
2.	(7) decibels	50 decibels

Columnellar Strut. Where there was no incus or insufficient long process to support a polyethylene sleeve, the continuity was re-established by means of a No. 90 polyethylene strut between the capitulum of the stapes and the tympanic membrane (Fig. 7).

RESULTS:	*Gain*	*Residual Bone-Air Gap*
1.	43 decibels	15 decibels
2.	27 decibels	10 decibels

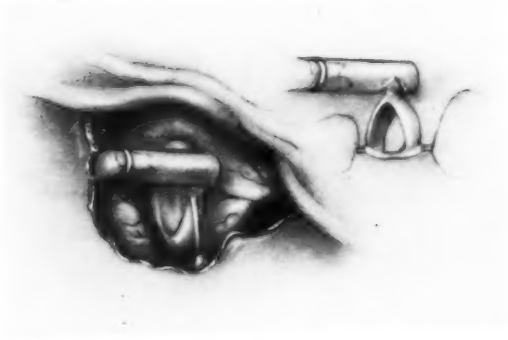

Figure 6

Figure 7

When it was impossible to re-establish continuity between the stapes and incus, the stapes crura were removed and a 90 polyethylene strut fashioned between the lenticular process and stapes footplate, or long process and stapes footplate (Fig. 4).

RESULTS:	*Gain*	*Residual Bone-Air Gap*
	1. 37 decibels	0 decibels
	2. 38 decibels	7 decibels

The last patient developed her 50 decibel loss in one ear after blowing her nose. Exploration revealed a small isolated cholesteatoma which had destroyed the incus completely. This was removed and the capitulum of the stapes connected to the handle of the malleus with polyethylene tubing. Hearing thresholds were essentially unchanged three weeks postoperatively.*

2. POSTINFLAMMATORY MIDDLE EAR DISEASE

This group consisted of sixteen cases divided as follows:

A. *Glue Ear.* One patient, aged 61, with a long-standing history of hearing difficulty which had increased slightly following a respiratory infection, a strong family history of hearing difficulty, and a conductive loss of 45 decibels, was found to have a glue ear without any adhesive process and aspiration restored the hearing to 12 decibels.

B. *Adhesive Otitis Media.* There were fifteen patients in this group with hearing losses of 22 to 52 decibels. Bone conduction varied from 2 to 7 decibels. History of significant preceding infection was present in approximately half of these, all eardrums were intact and scarring was absent or minimal.

In each instance gross thick inflammatory adhesions were found diffusely through the middle ear. These are not to be confused with the fine thin trabeculations which are almost uniformly found in the middle ear (Fig. 9). Several instances of partial or complete thin transparent membranous tents over the stapes were similarly excluded as not truly postinflammatory.

* (Fig. 8). This case was inadvertently omitted from the chart.

Figure 8

Figure 9

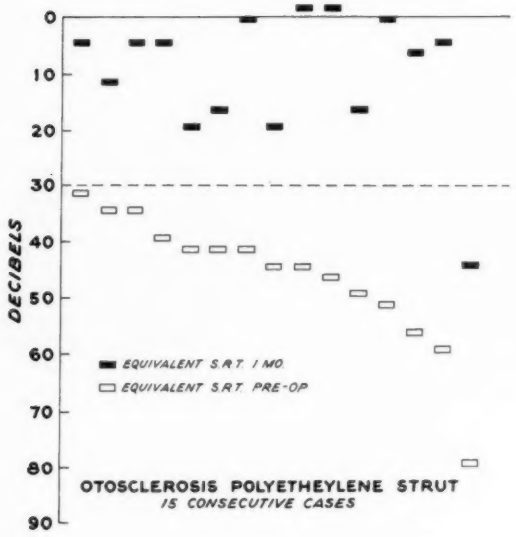

Figure 10

Surgical treatment consisted of careful sectioning of the adhesions and removal of hypertrophic scar tissue, followed by mobilization of the stapes either through the capitulum or footplate under audiometric control as described by Goodhill, until no further gain or a loss resulted. In each instance palpation of the stapes yielded a rubbery sensation which was quite distinct from bony fixation. It is noteworthy that most of these cases show a mild hearing loss. Only two were in excess of 40 decibels (Fig. 5).

The immediate surgical results varied widely from a gain of 35 decibels to a loss of 10 decibels. The postoperative result was even more erratic with 12 gains of from 8 to 35 decibels and 3 losses of from 4 to 13 decibels. Even in those cases with significant gains, there was a marked tendency to regress to the preoperative level, although in two cases a level of 12 decibels was maintained for one and for two years, and one for four years.

Figure 11

Figure 12

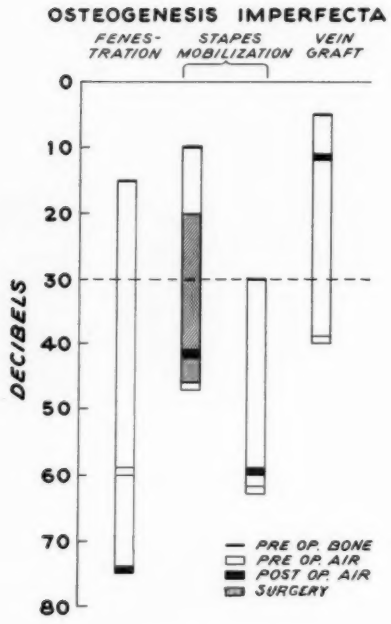

Figure 13

For the purpose of comparison, fifteen consecutive cases of otosclerosis treated by removal of the stapes crura, fragmentation of the footplate and insertion of a polyethylene strut are shown in Figure 10.

In these cases the losses were more severe, 32 to 85 decibels, and postsurgical audiometry showed more uniformity with seven cases having closed the air-bone gap, five having a gap of 10 decibels or less, and two showing a residual gap of 15 decibels. It would therefore seem expedient to offer a cautious prognosis where an adhesive process is suspect.

We have not seen any cases of diffuse tympanosclerosis with hyalin plaques within the mucosa, as mentioned by Goodhill,[1] nor

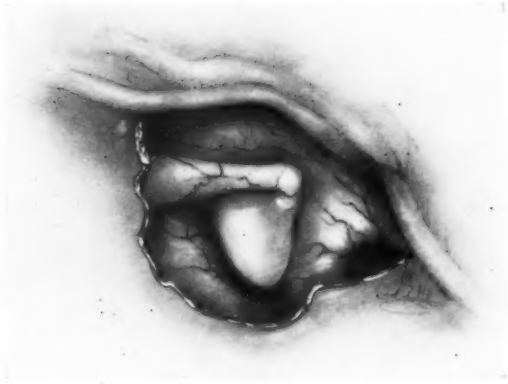

Figure 14

have we found any instances of diffuse fibrosis of the entire ossicular chain.

3. NON-OTOSCLEROTIC STAPES ANKYLOSIS

This group consists of two clinical entities:

A. Paget's disease (osteitis fibrosa) which appears late in life, and if it involves the skull, can be associated with a conductive hearing loss. Jenkins[3] reported three cases and concluded the pathological picture was dissimilar to otosclerosis. No cases of Paget's disease were seen in this series.

B. Osteogenesis Imperfecta (Osteopsathyrosis): This hereditary defect in bone structure, characterized by blue sclerae, frequent fracture and deafness, is associated with changes in the temporal bone closely resembling otosclerosis, and was clearly detailed by Van der Hoeve[5] in 1918 and is sometimes designated Van der Hoeve's Syndrome.

The bone fragility is most marked in early life and may occur ante partum with severe fractures at birth. The tendency towards

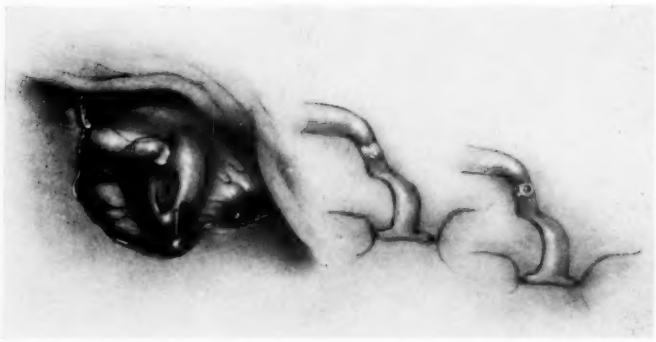

Figure 15

fractures improves spontaneously with puberty and may occasionally undergo remissions late in life.[6] Ruttin and Nager are said to have found typical otosclerotic foci in two such cases, while Nager found no histologic resemblance between the otosclerotic foci and osteogenesis imperfecta.[4]

Four cases of conductive hearing loss associated with frequent fracture and blue sclerae were explored; one by fenestration of the horizontal canal and three by tympanotomy.

Sections of the mastoid bone removed during fenestration are reported as follows: "The sections show three groups of bony trabeculae set close together. The trabeculae are wavy and delicate, they stain deeply eosinophilic, although some of the edges are bluish; the bone is well vascularized, the number of cellular lacunae appear slightly increased. Diagnosis: Trabecular bone consistent with osteogenesis imperfecta." This patient is a 22 year old female. A 33 year old male and a 33 year old female were explored and found to have marked hypertrophic changes in the fossa ovalis and stapedial footplate. The footplate area, although thickened, was composed of soft granular bone (Fig. 11) quite distinct clinically from the dense, hard bone seen in otosclerosis. A fourth case, a female aged 70, had similar hypertrophic changes, but these were undistinguishable from otosclerosis clinically.

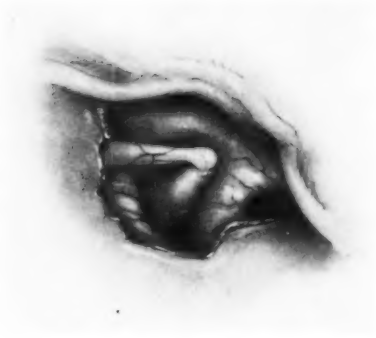

Figure 16

Surgical Management (Fig. 13).

1) Fenestration of the horizontal canal resulted in a good clinical hearing result which lasted less than one month and regressed to the pre-operative level. The first available audiogram was three years later and showed additional progression.

2) Chisel Mobilization: One case obtained 27 decibels increase at the time of surgery, but had lost all but 5 decibels by one month. The second patient obtained good mobilization with a round window reflex, but with no hearing gain at surgery or later.

3) Vein Graft (Shea Procedure) (Fig. 11): This resulted in 18 decibels increase at time of surgery and a level of 12 decibels at one month.

4. CONGENITAL ANOMALIES

Six patients comprise this group, which includes five with bilateral hearing loss, one with unilateral loss. Two felt their hearing loss was progressing. Three were children who had been hard of hearing since birth, two of these showed additional anomalies, e.g., congenital auricular fistulae in one and gross thumb abnormalities in the other.

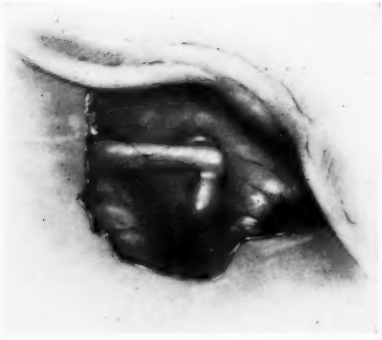

Figure 17

The ossicular defects in these were as follows:

CASE 1. A boy, aged 12, was found to have a marked constriction of the attic (Fig. 12), which completely enclosed a normal incus and malleus, and in addition the stapes was a solid plug-like object without the usual crura formation, and was firmly fixed to the region of the oval window (Fig. 14). Surgical enlargement of the attic and transmastoid mobilization produced no hearing gain. Subsequent fenestration of the horizontal canal showed a gain of 30 decibels with a residual bone-air gap of 18 decibels.

CASE 2. A girl, aged 16, showed a gross shortening of the long process of the incus with an attempt on the part of the stapes to bridge this gap with a resultant ½ mm fibrous incudostapedial joint (Fig. 15). The stapes was mobile and therefore the joint was opened and scarified and two pieces of five zero chromic catgut inserted into the loose joint space. At the end of one month there was a uniform gain of 5 decibels, and it is hoped there may still be more later. The residual bone-air gap is still 27 decibels, however.

CASE 3. A 12 year old boy had a normal incus and stapes but no stapedial margin (Fig. 17) similar to that described by House.[7] An attempt to create a footplate by multiple circumferential perforations released a tiny fountain of perilymph on the first perforation,

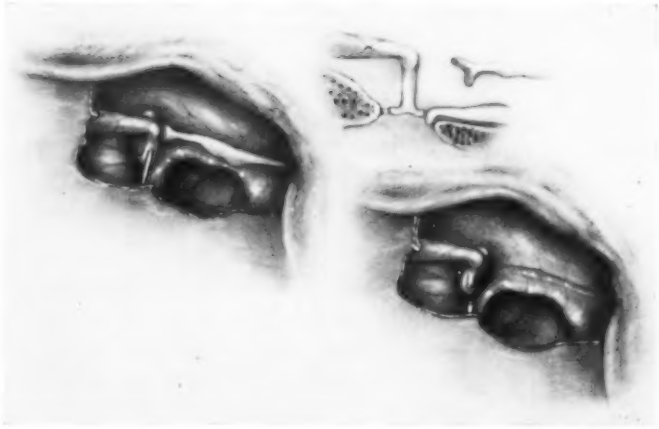

Figure 18

which rapidly filled the middle ear and canal. The defect was packed with gelfoam and a dressing applied. Several dressings were soaked in perilymph before the flow ceased spontaneously. Audiometry one month later showed a 5 decibel gain with a residual air-bone gap of 60 decibels.

CASE 4. A 46 year old housewife whose hearing loss dated back to childhood was found to have a similar deformity bilaterally. Chisel mobilization in each ear resulted in a gain of 5 decibels in one ear and a loss of 5 in the other ear. Secondary fenestration of the horizontal canal produced a gain of 30 decibels with a residual bone-air gap of 8 decibels.

CASE 5. A 37 year old female with a bilateral loss of 32 to 45 decibels for seven years was found to have monopodal stapes without any distinct margin (Fig. 16). Careful creation of an oval footplate by circumferential chisel cuts produced good mobilization and an initial improvement on the table of 30 decibels, which dropped in one month to within 5 decibels of the preoperative level. Exploration of the opposite ear showed conventional otosclerosis with a well formed stapes, and the air-bone gap was closed on this side at one month.

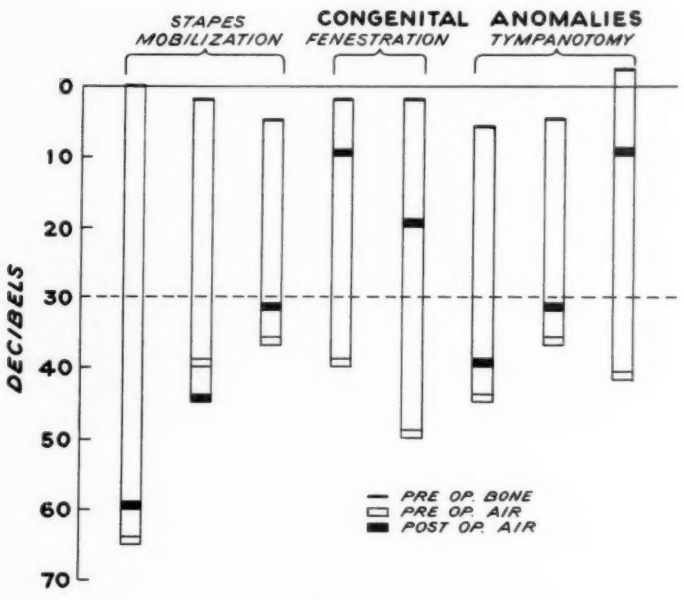

Figure 19

Case 6. A 38 year old Japanese male with a unilateral loss of 44 decibels since infancy was found to have a bony bar extending from the inferior margin of the stapes to the hypotympanum (Fig. 18). Careful removal of this bar and its retractor-like extension into the edge of the oval window resulted in a gain of 32 decibels with a residual air-bone gap of 12 decibels.

Congenital Anomalies (Fig. 19).

Results:	*Gain (loss)*	*Residual Bone-Air Gap*
Chisel mobilization	1. 5 decibels	60
	2. 5 decibels L	38
	5 decibels R	27
	3. 5 decibels	35

Fenestration of horizontal canal	4. 30 decibels	8
	5. 30 decibels	18
Removal bony bar	6. 32 decibels	12

Two additional cases of typical otosclerosis were found to have a total absence of stapedius tendon, muscle, and pyramidial eminence. Since this did not influence the surgical management, these are not individually documented.

SUMMARY AND CONCLUSIONS

A critical review of 1112 operative procedures for conductive hearing loss on 865 people with intact tympanic membranes reveals thirty-seven of these, or 4.2%, to have lesions other than otosclerosis. These are divided as follows:

	People	*Percent*
Incus defects	9	1.0%
Postinflammatory middle ear disease	16	1.9%
Nonotosclerotic stapes ankylosis	4	0.4%
Congenital anomalies	8	0.9%

The number of cases is too small to permit valid generalization, but the best hearing levels were obtained when it was possible to reconstruct a defective ossicular mechanism. Columnellar struts between incus and stapes gave slightly better closure of the air-bone gap than did columnellar struts from drum to stapes or incus sleeve procedures.

Adhesive otitis media was more unsatisfactory to treat in spite of several successful cases. Adhesions frequently reformed.

Nonotosclerotic stapes ankylosis associated with osteogenesis imperfecta was seen in four patients. No lasting hearing improvement was obtained from either fenestration of the horizontal canal or chisel mobilization of the stapedial footplate. Fenestration of the oval window with vein graft and polyethylene strut (Shea) resulted in normal hearing in the one patient on whom it was done.

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XLV

VEIN PLUG STAPEDIOPLASTY FOR HEARING IMPAIRMENT DUE TO OTOSCLEROSIS

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During the past several years, practices in stapes surgery have retraced the technical patterns laid down by Moit and others more than sixty years ago.[1] This repetition began in 1953 with the reintroduction by Rosen of the mobilization procedure.[2] Because of its inherent limitations, inevitable technical variations and modifications subsequently emerged simply because the mobilization method did not produce consistently satisfactory and lasting results. Regressions rapidly overtook the initial successes, reducing the numbers of sustained results appreciably. Direct approaches to the footplate using picks and micro-chisels to secure mobilization also failed to diminish the high incidence of regressions.[3]

Now, after six years, the next and final step in this historical replay of events is taking place—stapedectomy. Finally we have come full circle to the last act of stapes surgery which formerly led to its complete abandonment. Stapedectomy again is being done just as it was by Blake and Jack in this country many years ago, but with one very important difference.[4,5] This important difference was first suggested in 1876 by Kessel, who proposed replacing the footplate with a movable cicatrical membrane. Practical use of the idea was doomed to failure because among other considerations, the difficulties of removing the footplate safely were, for that time, unsurmountable.[6] The exposed oval window now is covered immediately with a membrane to prevent excessive perilymph escape and to protect the inner ear from external inflammatory invasion much as the tympano-meatal flap of

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the fenestration operation has been used to protect the labyrinth at the level of the horizontal semicircular canal.

Also an essential feature has been added—the creation of a firm link to rejoin the vestibular window to the remainder of the ossicular chain. This constitutes an incudo-vestibular arthroplasty, the principles of which have been used effectively by Shea and Schuknecht for reconstructing the sound carrying mechanism.[7,8] These innovations provide the previously missing link to the realization of a significant advance in otosclerotic surgery. The principles employed permit nearly all the required transducer characteristics of the middle ear to be restored with unusually consistent success in achieving hearing improvement.

Incudovestibular arthroplasty is effectively accomplished by an improved technique called "vein plug stapedioplasty." A section of vein four millimeters long and approximately two and one-half millimeters in diameter taken from the back of the hand is secured by a simple knot to a length of 5-0 gauge stainless steel suture wire measuring four and one-half millimeters (Figs. 1, 2). The resulting vein plug prosthesis is inserted into the exposed oval window niche with the distal end of the wire looped over the long process of the incus and crimped firmly in place (Fig. 3). This procedure provides adequately for several specific requirements for restoration of hearing among which are:

1. The preservation of a fenestra where the natural development of the hearing mechanism intended it to be, the oval window.

2. Application of a protective elastic covering over the oval window.

3. Substitution of a mobile membrane for the otosclerotically fixed footplate.

4. Restoration of the functional continuity of the ossicular chain.

5. Preoperative predictability of maximum hearing improvement with a higher degree of confidence than ever before.

These five accomplishments assure mobilization of the perilymph and endolymph, and in addition provide for what appears to be permanent maintenance of mobility.

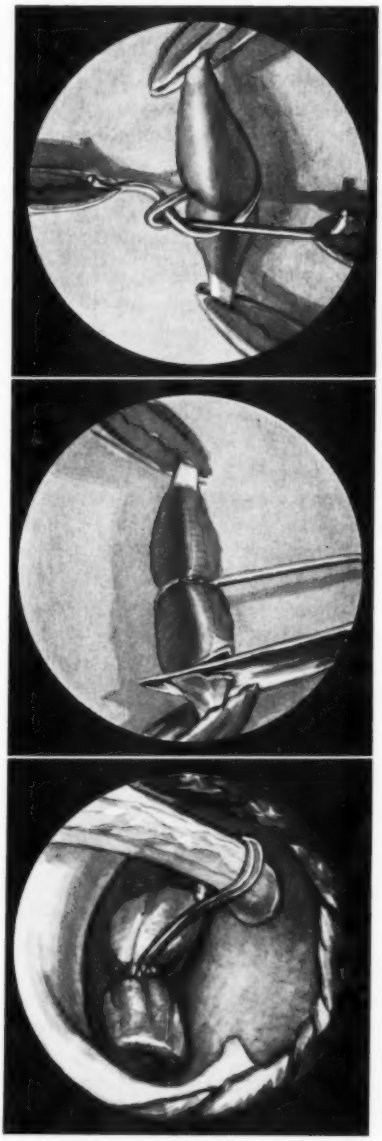

Fig. 1.—Section of vein held between forceps. Mid-section secured by simple knot of 5 or 6 zero stainless steel wire.

Fig. 2.—Length of vein trimmed to 4 mm after severing one extension of wire knot.

Fig. 3.—Vein plug inserted into oval window and secured to long process of incus, completing ossicular reconstruction.

RESULTS

Almost any comparison one could wish to make with the vein plug stapedioplasty technique reveals that its results of four to nine months' duration have exceeded all previous expectations. Exactly one year ago its was shown that the first 100 successful stapes mobilization procedures accomplished three to five years previously represented only a 49 per cent initial success rate according to success criteria which descended to a level of a fifteen decibel gain.[3] In other reports, as little as 7.5 and 11 decibel gains were submitted as successful results. Fortunately, attention to such small gains is no longer necessary because hearing gains with the vein plug procedure consistently surpass these figures considerably.

A measure of the maximum hearing gain postoperatively is the reduction or elimination (closure) of the difference between the puretone air and bone conduction thresholds. This difference may be referred to as the air-bone gap. Among the first 100 mobilization successes, there were only 25 air-bone gap closures* which were eventually reduced to 18 by reankylosis of the footplate.

Air-bone gap closures now are so regularly achieved with the vein plug technique that they constitute practically the only important measure of success. Whether the hearing improvement results in a puretone or speech reception level of better than thirty decibels depends on the actual level of preoperative bone conduction thresholds.

One-hundred consecutive vein plug stapedioplasties accomplished between May and November, 1959, produced the striking success rate of 90 air-bone gap closures. (Comparing postoperative bone with postoperative air conduction thresholds only one more air-bone gap closure is added to the results.) (Fig. 4). Eighty-six or 95 per cent of these achieved hearing acuity of better than an average 30 decibels in the speech range of 512, 1024 and 2048 frequencies. Further analysis reveals that 76 or 85 per cent of the 90 ears reached a hearing acuity of better than 20 decibels; and 52 or 58 per cent of the 90 ears resulted in a hearing acuity of better than 10 decibels. Hence,

* Closure of the air--bone gap is defined as an average difference of ten decibels or less between the preoperative bone conduction and the postoperative air conduction at 512, 1024 and 2048 cycles per second.

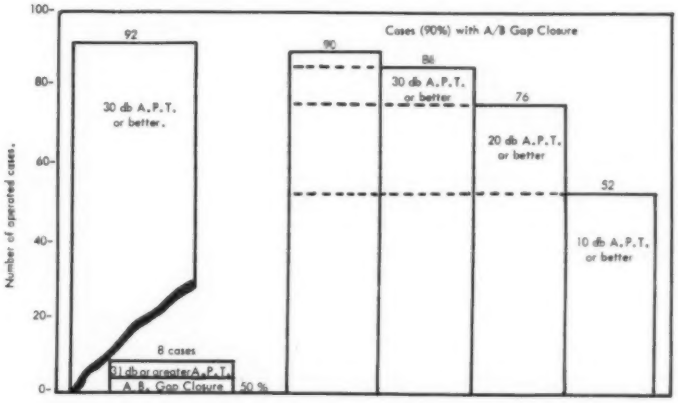

Fig. 4.—Audiometric results of the first 100 consecutive (vein plug) stapedioplasty operations.

more than one-half of the entire 100 operations produced a hearing threshold which may be considered normal. Despite the failure of 10 operations to produce air-bone gap closure, 6 achieved a hearing threshold of better than 30 decibels (Table I). Practically all of the pathological variations of oval window otosclerosis, ranging from limited anterior footplate involvement to solid footplate incarceration with overgrowths from the promontory and sub-facial abutment were encountered in this series. Nearly 40 per cent of them were of the latter variation.

Turning back again to the results of the indirect and the direct footplate techniques, it will be noted that regression of hearing rapidly took away the impressiveness of initial success. Regressions among the indirect stapes mobilization group were reported to be 28 per cent, most of them occurring within three months postoperatively. In a group of 178 initially successful direct footplate mobilizations, the regression rate was found to be 38 per cent.[3]

By comparison, only two of the vein plug procedures have shown a partial regression in three months. One is accountable to an inadequate connection of the prosthesis to the long process of the incus but

TABLE I

POSTOPERATIVE DATA ON 10 EARS WHICH DID NOT ACHIEVE AIR-BONE GAP CLOSURE

NO. OF CASES	POSTOPERATIVE AIR-BONE GAP	POSTOPER. AVG. A.C. THRESHOLD	COMMENTS
1	11 db	13 db	None
1	12 db	15 db	None
2	(a) 14 db	17 db	None
	(b) 14 db	17 db	None
1	15 db	27 db	Loose connection
1	16 db	18 db	None
1	22 db	45 db	2/3 footplate not removed Fenestra too small
1	30 db	38 db	1/3 footplate not removed Fenestra too small
1	36 db	58 db	3/4 footplate not removed Fenestra too small
1	40 db	63 db	Round window closure ?

still has a 27 decibel threshold. The other is believed to be due to failure to remove one-third of the footplate. No other regressions have occurred in the vein plug series, which suggests at least, that there is very little evidence of a trend to regressions within four to nine months postoperatively. One operation produced no change in the hearing threshold presumably because of round window occlusion which was suggested by observing marked narrowing of the niche at the time of surgery. It is presumed that two failed to achieve appreciable hearing improvement because of inadequate exposure of the oval window. Considerable portions of the footplate were not removed in both cases (Table I).

COMPLICATIONS

There have been no serious complications. Three patients developed otitis media during the first postoperative period of three weeks, all of which were sustained without evidence of labyrinthine disturb-

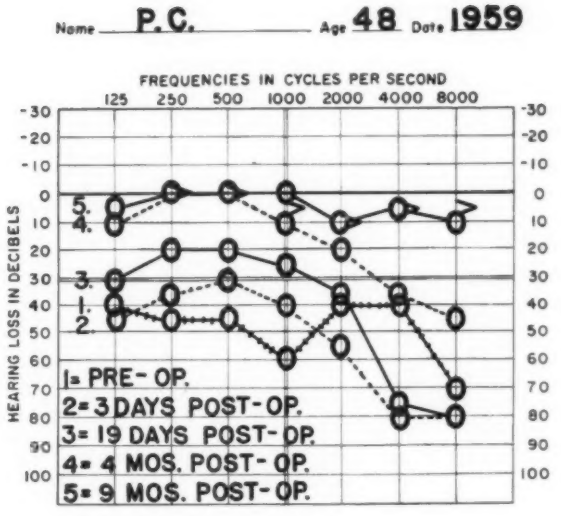

Fig. 5.—Typical postoperative audiometric pattern of hearing recovery.

ance and without compromising the maximum hearing gain. There is no instance of the hearing made worse. Vertigo, generally mild, is usually confined to the first three days postoperatively, although it may persist as an occasional postural disturbance for six weeks. Tinnitus, which is described as high pitched, may be quite severe for ten to fourteen days, but usually does not persist beyond six weeks.

The tinnitus may be explained by the audiometric pattern of hearing recovery. The air conduction audiogram at three days postoperatively frequently shows an improvement for low tones and sometimes a severe loss for high tones. The bone conduction thresholds remain fairly stable. While hearing for the speech range is usually achieved by the third week, improvement of hearing for the high tones continues for at least six months (Fig. 5). This peculiar fact may be attributed to physical changes taking place in the vein plug. Certain other possible correlations have not yet been completely evaluated.

TECHNICAL DIFFICULTIES

Some of the more common technical difficulties are encountered in creating and placing the vein plug prosthesis. It is recommended that the prosthesis be made before exposing the middle ear so that in the event the operation is prolonged because of an obstinate footplate the local anesthetic effectiveness of about one hour will be adequate.

The difficulty of crimping the wire loop around the long process of the incus is virtually eliminated by carefully making the loop so that the dimension of the horizontal segment of the loop is not more than one millimeter, and the short arm of the loop is at least two and one-half millimeters long—a sufficient extension to permit the engagement of a properly designed crimper* (Figs. 6, 7). In other words, the loop should fit onto the long process of the incus snugly so that very little crimping is necessary to make the prosthesis secure.

The footplate is not perforated nor is any part of it removed until the field is rendered bloodless. Bleeding into the vestibule is prevented by first removing every vestige of mucous membrane over the otosclerotic footplate and surrounding margins of the oval window niche. Gelfoam pledgets saturated in topical thrombin and neosynephrine applied to the field of operation help to control capillary bleeding. The footplate then may be removed piecemeal or in sections with specially designed picks without the risk of excessive hemorrhage (Figs. 8, 9). In the event hemorrhage does occur, aspiration should be avoided because it is likely to displace the perilymph with the overlying blood and cause the blood to gravitate into the vestibule. This may be harmful to hearing function. When the blood coagulates, most of the clot may be teased out of the niche with picks or scrapers. A thin layer of clotted blood may be permitted to remain over the oval window and the vein plug inserted over it without compromising maximum improvement of hearing.

In order to obtain maximum exposure of the oval window, very sharp micro-scrapers are used when necessary to shave off otosclerotic projections from the promontory and subfacial abutment. Invariably the most extensively involved stapedio-vestibular joint may be out-

* Modified after Schuknecht and jointly designed by H. L. Williams, J. B. Gregg, and C. M. Kos.

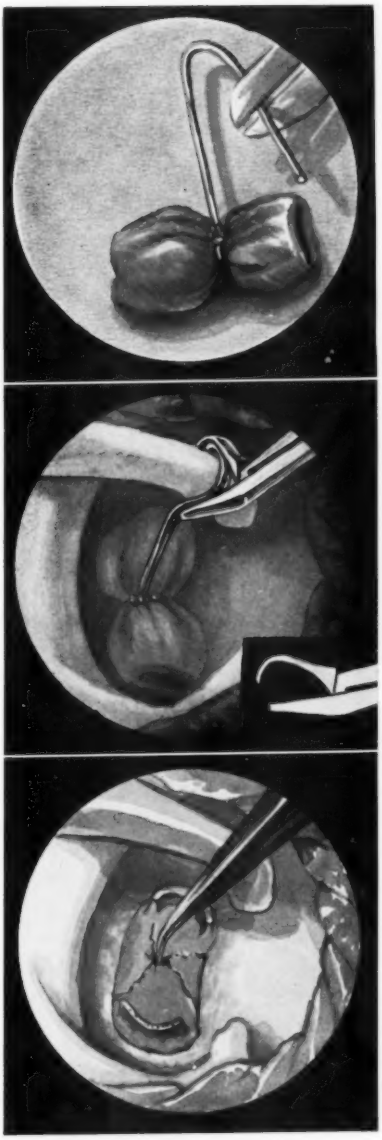

Fig. 6.—The wire is bent into a loop 4½ to 5 mm from the end of the knot. The loop is not more than 1 mm in diameter. The short end of the loop is at least 2½ mm long.

Fig. 7. — One of several Schuknecht type crimpers used to secure wire loop to long process of incus.

Fig. 8.—Footplate perforated at its thinnest point with Kos offset picks.

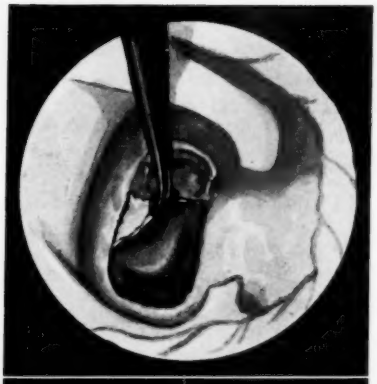

Fig. 9. — Footplate removed in sections with Kos offset pick or spatula.

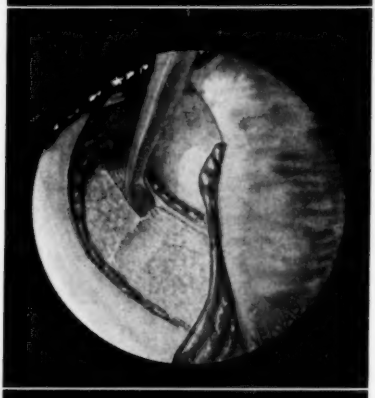

Figure 10

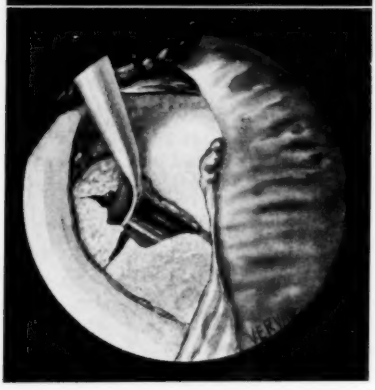

Figure 11

lined in this manner, and the thickest footplate reduced to a degree of thinness which permits its removal in two or three segments with relative ease (Figs. 10, 11).

Probing desperately for fragments of the footplate risks irreversible damage to the cochlea. The entire footplate, or fragments thereof may recede into the vestibule and still be covered with the vein plug without reducing the chances of appreciable hearing improvement.

CONCLUSIONS

Personal dissatisfaction with the results of a statistical analysis of over 1,000 stapes mobilization procedures led to the development at the State University of Iowa of the vein plug stapedioplasty technique in May of 1959. At first it was employed cautiously only in those cases which failed to achieve or maintain hearing improvement following one to four previous mobilization operations. When it became obvious six weeks to three months postoperatively that the results favorably exceeded in every respect those of formerly employed techniques, vein plug stapedioplasty was established as the routine procedure for otosclerotic hearing impairment. Consequently, the previously used fenestration and mobilization operations have been abandoned. Now, nearly one year later, nothing unfavorable has occurred to suggest that such action should have been otherwise.

However, the vein plug technique is not recommended for general acceptance because of the relatively short duration of experience with it. A number of initially anticipated problems still may arise to alter drastically current impressions of its value, but so far, there has been no requirement to face them.

An analysis of 100 consecutive vein plug stapedioplasty procedures reveals that ninety achieved (air-bone gap closure) maximum hearing improvement permitted by the function of the hearing nerves as measured by puretone bone conduction. Fifty-two of these resulted in essentially normal hearing (0 to 10 decibels). Of the 10 which did not result in air-bone gap closure, 6 produced hearing thresholds of better than 30 decibels in the speech range. Despite the possible tentative nature of the preliminary results reported here, the superior-

ity of them over the results of previously employed techniques indicates a potential achievement of success heretofore unattainable.

UNIVERSITY HOSPITALS

Compiling data and maintaining records is gratefully credited to Thomasine Campbell, M.A., J. Shapley, Ph.D., and William Prather, Ph.D., of the Section of Audiology.

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XLVI

PARTIAL STAPEDECTOMY

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Microscopic surgery for the restoration of hearing in conductive lesions has revolutionized otology. In the last few years, our surgical attention has moved to the pathologic area of the ankylosed stapes.

At the beginning of this paper, it seems reasonable to suggest certain aims for surgery on the stapes for otosclerosis that they may be applied in formulating procedures that will be developed in this presentation. These aims are not new since in all surgery two major principles are well recognized and can be said to be paramount. These two great principles are:

1. Removal of the diseased part.

2. Preservation of normal tissue in a functional state.

Although compromise of these principles is frequent, it is believed that they must be applied to all techniques on the stapes.

Many fine past procedures on the stapes have given a high percentage of excellent results. Desire for improvement, however, drives all otologists to continually analyze their position in relation to perfection. A critical analysis under the guide of the above stated principles indicates deficiencies that seem apparent in many of our techniques. For example, a simple mobilization of the stapes, although it preserves the normal stapes, does nothing to remove the pathology or prevent its interference with later function. On the other hand, the opposite extreme is true in the total stapedectomy which immediately begins by destroying the entire normal head, neck and crural arch of the stapes. This destruction is a contradiction to the above principle of preservation of normal tissue in a functional state. The pathol-

ogy as a rule does not involve the head, arch, or crura of the stapes and their removal neither removes the pathology nor does it enhance the functional result. It is suggested in this paper that this removal of normal tissue may be needless if other mechanical approaches can successfully accomplish hearing restoration.

THE NEED FOR FLEXIBILITY IN SURGICAL PROCEDURES

If pathology is to be removed and normal tissue is to be preserved in a functional state, it is apparent that there must be different approaches to different problems in different ears. The idea of one operation for all ears seems desirable, but it is quickly apparent that no one surgical technique meets all the needs of the pathology encountered in the region of the stapes. The variety of lesions which cause deafness of a conductive nature demands that the otologic surgeon be extremely flexible. His mind and his instrumental armamentarium must be prepared to do a large variety of techniques. The unveiling of the middle ear by lifting the curtain of the tympanic membrane reveals variations as marked as those seen on the human face. No one technique will meet the high requirements which would be set for all cases. This is evidenced by the following:

1. Gross otosclerotic infiltration of the footplate may involve a small rim area or, when advanced, change the anterior portion of the footplate into heavy otosclerotic bone and leave the remainder quite thin and normal. Isolated posterior infiltration of the footplate of the stapes by otosclerosis is far less common than anterior involvement. This does, however, occur. Smooth otosclerotic infiltration of the entire footplate of the stapes and annular ligament so as to obliterate all fenestral and footplate identification may be seen. It seems unreasonable that all these varieties should be treated alike.

2. The histologic characteristics of otosclerosis are important. For instance, a small ivory-hard otosclerotic focus which has invaded only a small portion of the footplate may produce a severe loss of hearing for many decades by firm stapedial fixation; whereas, paradoxically, a mountainous extremely bulky, but soft, otosclerotic invasion of the footplate may produce only a mild to moderate hearing impairment. Despite its mass, the soft focus may allow partial transmission of vibrations. Preoperative evaluation thus far cannot accurately predict

what will be encountered at the time of surgery.[9] This emphasizes the present necessity of the surgeon's being prepared for any variation in technique which may be in order to correct the wide variety of possible pathologic conditions to be found in any one ear.

3. The mechanical problems presented by anatomical and congenital variations of the structures of the middle ear also demand a flexible approach.[9] An extremely deep niche, or a footplate obscured by congenital malformation, or an obscuring overhang of the facial nerve, are only a few of the numerous anatomical variations which demand consideration when a surgical solution is being formulated.

The surgeon should exercise courage to undertake the most formidable procedure. He should also be prepared to be conservative in the preservation of all apparently normal tissue. If mistakes in evaluation occur and a so-called normal segment of the stapes later fixes, the otologist should remember that the drum may be elevated and the middle ear re-entered within a matter of a few minutes and the operation resumed in a place where it was originally terminated. By all means, he should be in a position of rapport with his patient which would allow this continuation at a later date, if necessary.

SIGNIFICANCE OF TRENDS IN SURGERY ON THE STAPES

During the past few years, it has been increasingly apparent that the trend of surgery on the stapes has been toward more radical procedures. In general, this trend has produced two surprising results: 1) better long term results; 2) very few complications.

These are called surprising results because no one would have dared predict this only a few years ago.

Procedures on the stapes have become more radical in two areas: first, above the footplate and, second, below it.

Instrumentation in the labyrinth a few years ago was considered to be impossible without producing severe damage to the cochlea. Although some ears have been damaged by accidental injury through labyrinthine instrumentation, an extremely few have been harmed compared to the large number who now have been restored to service-

able hearing. The radical procedures below the footplate may be said to be good if exercised with restraint. The resistance of the labyrinth to trauma and the ability of the tissues to restore order have been a welcome surprise to otology.

Radical procedures above the footplate, however, are challenged in this presentation. Although removal of the entire stapes seems to be necessary at times, the principle of preservation of normal structures mentioned above demands a critical analysis of any destructive entry which would sacrifice the normal portion of the stapes as a functional unit.

During the past two years it has seemed desirable to overcome some of these problems requiring removal of the normal stapedial head, arch and crura. It is, therefore, the purpose of this paper to present an outline of techniques which the author has found useful. These steps are presented without the assumption that they meet all the known requirements mentioned in the principles above. It is not suggested that these procedures should replace entirely all other well recognized procedures on the stapes. Rather, they are simply suggested as technical steps toward an idealistic goal.

THE BASIS OF PARTIAL STAPEDECTOMY

Partial stapedectomy means removal of a portion of the stapes.[11] It means the removal of the pathologic segment of the stapes. Furthermore, if one removes only the pathologic segment of the stapes, by implication, the normal portions of the ossicle should be left in a functional state.

Otosclerotic fixation of the stapes may be divided into three groups: 1) anterior fixation; 2) posterior fixation; 3) complete otosclerotic fixation of the entire stapes. This includes all ears from moderate bipolar involvement to diffuse otosclerosis involving the entire footplate.

A partial stapedectomy procedure will be described for each of these groups and then consideration will be given to the treatment of those ears wherein mechanical results require a deviation in technique.

PROCEDURE

ANTERIOR SEGMENTAL REMOVAL: PARTIAL STAPEDECTOMY

Figure 1

First, a quick summary of the entire procedure will be given and, following this, a step-by-step description will be made with comments in detail. Briefly, the procedure for removal of the anterior segment is as follows:

1. Obtain proper exposure.

2. Transect the footplate of the stapes posterior to the pathology.

3. Cut the anterior crus.

4. Free the pathologic segment.

5. Lift the pathologic segment out of the window.

6. Mobilize the posterior segment.

7. Close the labyrinth by covering the newly created orifice with gelatin sponge or gelatin film (Gelfilm or Gelfoam).

8. Replace the tympanic membrane and skin flap to their original positions and apply the routine external canal dressings.

ELABORATION OF TECHNIQUE AND DISCUSSION OF PROCEDURE

1. Technique of Anterior Partial Stapedectomy

Otosclerosis involving only the anterior half of the stapes is by far the most commonly encountered cause of fixation of the stapes.[3]

The diagnosis of location or the amount of otosclerosis prior to surgical exposure is impossible by any known means. Indeed, even at the time of operation, the exact extension of the otosclerosis cannot be determined with anything short of a cell by cell study under high-powered microscopy. Until this is possible in surgery, decisions must be made forthrightly with evidence that can be seen through the Zeiss operating microscope under powers up to 40 times. Fortunately, results are extremely good despite these limitations.

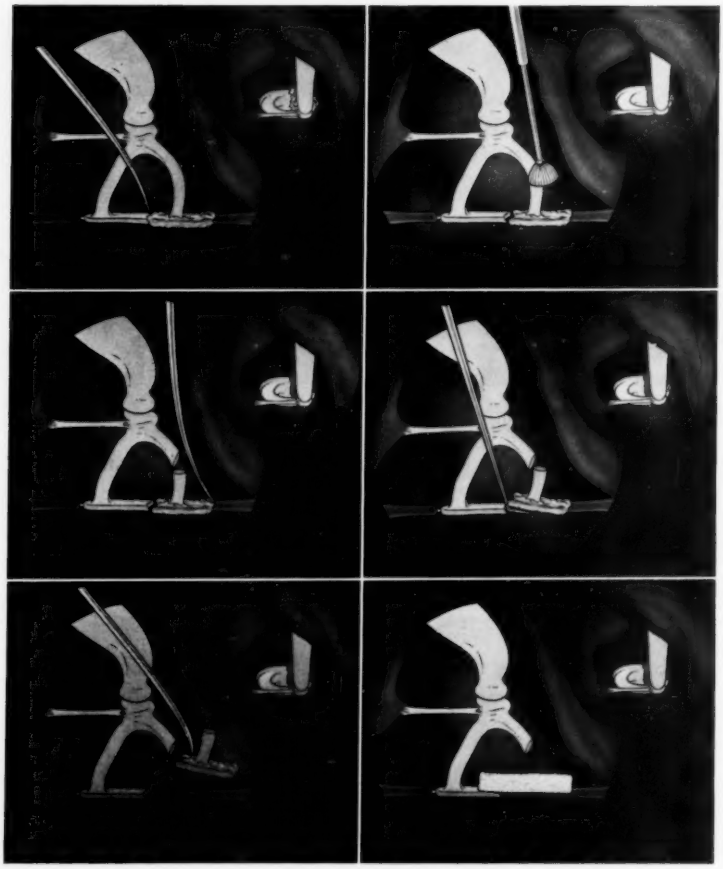

Fig. 1.—Anterior partial stapedectomy.
(The sequence of these diagrams is: upper left, upper right, middle left, middle right, lower left, lower right.)

STEP NO. 1. *Exposure.*

Since this surgery requires an operative analysis of the otosclerotic extension, the highest degree of exposure must be obtained. If a stapes is fixed, one can usually assume by the evidence of statistical chance that the anterior segment is involved in the pathological process. Exposure of the posterior segment for analysis is, therefore, extremely important. This, fortunately, can be done to a reasonable degree in most ears.

Improvement in exposure may be obtained by the following methods:

a. Removal of a large amount of bony overhang.

b. Moving the head of the patient and the microscope in various positions to permit viewing of the footplate from various angles. The head of the patient, the speculum, and the microscope should not be fixed. It is amazing how many areas can be seen well if the head is moved to a slightly different position or the microscope is inclined at a slightly different angle.

c. By cutting the stapedius tendon, better visualization of the posterior crus and the posterior margin of the footplate may be obtained.

d. A better view of the crura and footplate may be obtained by shifting the incus forward or backward within the limitations of the incudostapedial joint.

e. On occasions, it may be necessary to sever the crura at the footplate and move the arch to one side to permit sufficient visualization of the footplate area. When in doubt, this should be systematically carried out keeping in mind that the posterior crus should be maintained in length for future reconstruction after the pathology has been removed. This is seldom necessary in the technique for anterior segmental removal.

STEP NO. 2. *Transect the footplate of the stapes posterior to the pathology.*

After carefully examining the otosclerotic infiltration of the stapes, penetrate the footplate gently with an extremely fine pick.

Make from three to six small holes producing a line across the footplate separating the pathologic area of the stapes from the normal. The line of penetration should be well within the normal bone as is determined by careful high-powered microscopic examination. If the otosclerotic invasion seems to extend along the superior or inferior margin of the footplate, the line of transection should be made to include all known pathologic bone on one side of the line. In using the fine pick for making a perforation of the footplate, take care that the pick does not penetrate too deeply into the labyrinth. By turning the pick a few times in a burring fashion as it rests on the footplate, the desired perforation may be accomplished without exerting dangerous pressure. After the line of transection has been carefully mapped out by three to six perforations extending across the footplate, make a clean cut through the bone between the perforations with a fine chisel. Again, take care not to enter the labyrinth deeper than is necessary. The footplate has now been divided into a normal posterior segment and the anterior segment containing pathology.

STEP NO. 3. *Cut the anterior crus.*

Numerous methods and instruments for cutting the anterior crus have been studied and tried. Two instruments are now recommended. The first instrument of value is a half-sphere cutting burr. This instrument was originally suggested by Guilford.[7] For better visualization, the shaft of the burr has been reduced in diameter. This burr may be used on a regular Wullstein contra-angle handle, or, even more simply, on a Shea-Richards hand drill. There should be three sizes of burrs on the instrument table: .5 mm, 1 mm and 1.5 mm. If the surgeon can see the entire anterior crus, the burr may be used anteriorly. Frequently, the burr can be used on the side of the crus either superiorly or inferiorly. The drill must be handled with extreme delicacy. Very little action of the burr is needed. As soon as the burr very lightly engages the bone it changes color due to the burr picking up bone in its teeth. Since it requires so little to cut the crus and since it offers no palpable resistance, this may be the only signal of engagement of the instrument on the crus. If carefully used, the anterior crus can be cut with no fracture disturbance of the posterior crus. This is by far the safest instrument for cutting the crus in the author's experience. The second instrument of value is one with a strong sharp flat rounded surface at the end. The shaft is curved in a triple angulation. These angulations were carefully meas-

ured and designed so that good visualization of the working area can be constantly maintained. We nicknamed this instrument the "whirlybird" because the name communicates a rapid identification. It is an excellent utility instrument in partial stapedectomy. Frequently, it will be necessary to complete the lysis of the crus by using the sharp edge of this instrument. By using the burr and the whirlybird an accidental fracture of the posterior crus is now very rare.

STEP NO. 4. *Free the pathologic area of bone.*

A small thin gouge is placed anteriorly to the anterior crus at what appears to be the junction of the otosclerotic bone with the normal bone. This cannot always be accurately determined, but accurate positioning is not always necessary. With gentle pressure exerted on the gouge, the handle is slightly twisted in a rocking fashion. The pathologic segment of the footplate may be seen to start moving. The purpose of this maneuver is not to cut through the otosclerotic focus, but to rock it free. It is amazing how many times so little effort causes beginning motion. This is reasonable in the light of known histopathologic knowledge of the structures involved. Kelemen[14] states that, "The line of demarcation between the normal bone and otosclerotic bone is as sharp as a razor." Tweddle,[16] Drury[5] and Hagens[8] as well as many other histopathologists describe this sharp line of demarcation. There is actually a microscopic separation between the two types of bone. As is stated by Hagens,[8] the bone adjacent to the otosclerotic focus typically appears rarefied. There is a crevice-like gap, which he terms a "fracture line," between the edge of the focus and the adjacent bone. It is not unusual, therefore, to observe movement of a large area containing the otosclerotic focus, the attached footplate and the stump of the anterior crus.

Very rarely, the fixation is so firm or the stapes is so wedged in its position that digital manipulation to be successful would require a dangerous amount of pressure. In this event, it is best to use the gentle tapping caused by the prongs of a vibrating 128 steel tuning fork on the handle of the gouge. This will cause the pathologic area to begin to shake loose. This method was suggested by Farrior.[6] The amount of effective vibration caused can be deliberately controlled by the tight squeezing of the fingers holding the gouge.

Since the entire segment may suddenly break free if strong inward pressure on the instrument is used, one must be careful not to

allow subluxation of the entire anterior segment. Before motion can be stopped, it is possible to push the anterior segment into the labyrinth and thus allow it to become an irretrievable object. Once slight motion of the segment is obtained, it is remarkable how easily the entire segment may be lifted out of the oval window as if encapsulated.

STEP NO. 5. *Lift the pathologic area of bone out of the oval window.*

The footplate margin of the anterior segment can usually be seen clearly at the edges produced by the transection cut made in Step No. 2. Insert an extremely fine specially made right angle, or 45 degree angle, pick in the transection cut and just as it enters the labyrinth rotate it so that it slides under the anterior segment of the footplate. Lift this segment outward and anteriorly until a goodly portion of it is seen presenting itself anteriorly. One is usually amazed how large the mass of bone appears as it is being removed.

Even though these fine special instruments are strong, one should never exert more than the most gentle pressure when lifting the anterior segment outward. The attached portion of the stapes should be easily movable. If it is not and stronger lifting pressure is desired, a special flat right angle, or 45 degree angle, footplate excavator should be used. This instrument is strong enough to withstand considerable pressure and thin enough to slide under the anterior pathologic segment without occupying excessive space in the labyrinth. It is made much like a hoe and is extremely useful in all surgery on the stapes. After the pathologic segment has been partially delivered out of the oval window and is visible anteriorly, a fine curved pick may be used to tease the segment out on the promontory where it may later be removed with forceps.

As the pathologic segment is being removed from the window, one is impressed by, first, its size, second, how easily it shells out in one piece and, third, how it usually leaves all mucous membrane behind as if submucosally dissected free.

STEP NO. 6. *Mobilize the posterior segment.*

Good visualization is necessary for proper analysis and instrumentation in this area. Occasionally, in order to obtain a good view

of the posterior crus and footplate, it is necessary to cut the tendon of the stapedius muscle. The tendon should not be cut unless necessary since it can be proven to remain active throughout years of severe ankylosis of the stapes. Its activity is often easily seen when instrumental sounds are made in the ear during an operation. It is unreasonable, therefore, to assume that it is useless because of fibrosis or chronic spasm, etc. Although perhaps poorly understood, the function of the stapedius muscle must be considered to be a worthy one.[10]

Due to the discriminatory separation of the pathologic area of bone from the normal area of bone, the posterior segment should now be free of otosclerosis. However, because of fixation from disuse this portion of the stapes should not be considered to be in a normal physiologic state whereby it can transmit normal vibrations from the incus to the labyrinth. The fixation of the posterior segments from disuse may be caused by excessive fibrosis of the annular ligament or perhaps even by calcification of cartilaginous rest cells in the ligament during periods of disuse. These cartilaginous rest cells are embryologic remnants of the developmental period of the lamina stapedialis and may become ossified in the middle decades of life much as cartilage in other regions of the body undergoes such change.[9] Non-otosclerotic fixation might thus occur. Because of variable fixation, the posterior segment should, therefore, be mobilized.

To mobilize the posterior segment, a very fine pick is inserted into the annular ligament. After lysis is begun, the posterior segment with its attached crus and footplate should be gently pushed forward. This causes a repositioning of the posterior segment to occupy the central area of the window.

STEP NO. 7. *Close the labyrinthine orifice with gelatin sponge or gelatin film (Gelfoam or Gelfilm).*

One has now produced a large defect anteriorly by removing the pathologic bone. Another moderate defect has been produced posteriorly around the edge of the remaining footplate. A new annular ligament will be rapidly formed covering these areas. It will be composed of a thin membrane of endosteum and mucous membrane. This forms very rapidly to produce protection for the labyrinth and closure of the fluid hydraulic system.

Frequently, there is enough mucous membrane remaining to cover completely, or partially, the fenestral orifice. With the right angle excavator, tease this mucous membrane into position over the orifice.

During the healing period, it is necessary to close the labyrinth by covering the fenestral orifice with gelatin sponge or gelatin sheet (Gelfoam or Gelfilm).

Gelatin sponge (Gelfoam) absorbs in from three to four weeks and provides a perfect covering during this time. It is best used after highly compressing it and manipulating it into position with a chisel.

Gelatin sheet (Gelfilm) is composed of the same absorbable material as Gelfoam, but it is solid and comes in a very thin clear sheet. When cut to size it forms an adherent covering over the fenestral orifice for approximately two months. It does not conform well to a rough topography and, therefore, should be used only when dealing with a nearly flat surface.

In times past, we have held fear that this labyrinthine opening would remain patent and thus allow exposure of the labyrinth to disease as well as to allow escape of perilymph through a fistula into the middle ear. By experimental as well as clinical evidence, we now know that this window, not much larger than the head of a pin, will be covered by mucous membrane and endosteum very rapidly. This is particularly true if proper protection is given during the healing period. In 1931, Brunner[4] reported a case in which bilateral mastoidectomies had been done twenty-one years before death from other causes. Examination of the temporal bones showed that the stapes had been luxated on both sides during the operation. Both windows were closed by dense connective tissue membrane. There were no changes in the inner ear demonstrating that even under very critical healing conditions the oval window closed without producing degenerative changes in the inner ear.

We have recently reported a case where the temporal bones were obtained thirteen days after stapedial surgery and in spite of the relatively short time which had elapsed since the operation, which fenestrated the oval window, the continuity of the endosteum was already almost completely restored.[1] This is also in good agreement with the

experimental findings in cats reported by Bellucci and Wolff in which the oval window was already covered with thin membrane three days after stapedectomy.[2]

It is believed by the author that the fluid of the labyrinth provides a perfect bed for the advancing sheet of epithelium and the surface tension of the fluid provides a guiding force for directional growth. It is further considered probable that the covering of the fenestral orifice is complete in the human within 24 to 72 hours. When we remember how rapidly the large denuded surface of the tonsillar fossa is covered with mucous membrane following tonsillectomy, our fears diminish regarding this dehiscence in an area not much larger than the size of the head of a pin.

If the orifice of the labyrinth is considered by the surgeon to be too large to depend upon natural covering from the processes of membrane healing, several alternatives are present.

1. One may use the vein graft technique suggested by Shea.[15]

2. One may use a pinhead-sized soft tissue graft from the subcutaneous surface of the tympanomeatal flap to cover the defect as has been reported by the author. This is very easy to obtain and does not require the opening of a new surgical field. The superior part of the tympanomeatal flap is usually thick and with curved Wullstein scissors a tiny piece of subcutaneous tissue may be obtained to cover the labyrinthine defect.[11]

3. As suggested by Schuknecht, a tiny piece of fat can be obtained through a small postauricular, or lobular, incision. The fat can then be used to cover the defect.

The author has used these methods, mentioned above, but now prefers to cover the area as much as possible with the original mucous membrane followed by tight closure with Gelfilm or Gelfoam. The experience of House as well as that of the author seems to indicate that the soft tissue graft covering is superfluous whether it be vein, fat, or subcutaneous tissue.[12,13]

If the posterior segment of the normal stapes has been transpositioned toward the central area of the window, it is well to place a small

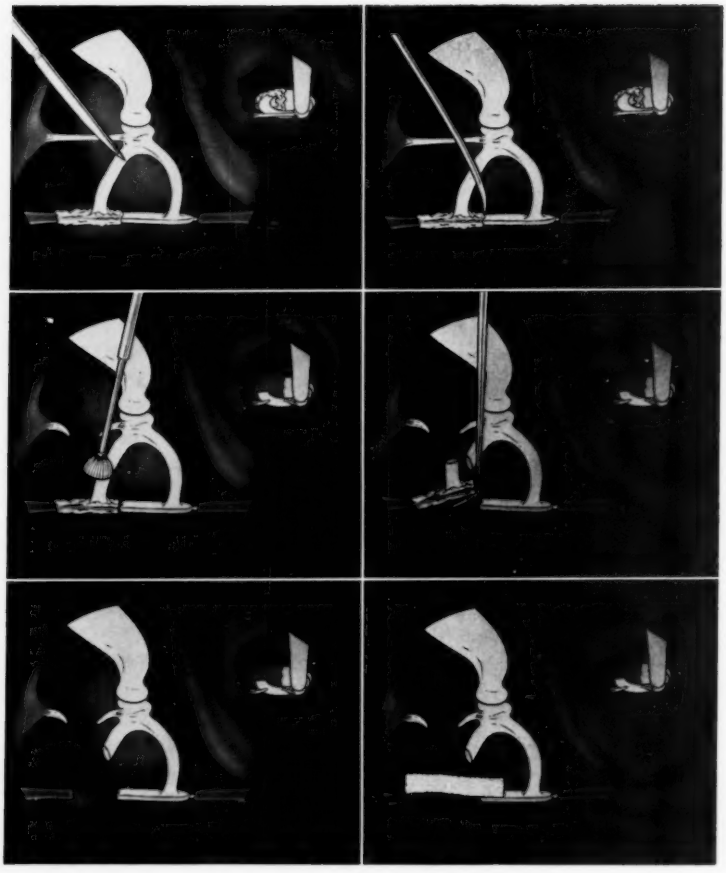

Fig. 2.—Posterior partial stapedectomy.
(The sequence of these diagrams is: upper left, upper right, middle left, middle right, lower left, lower right.)

piece of Gelfoam behind the posterior crus in order to secure it in this position until healing occurs.

The new, wide, annular ligament is composed of a thin membrane of endosteum on the labyrinthine side and mucous membrane on the tympanic side. It is believed that this new membrane covering provides a more adequate protection against the future ankylosis of the remaining stapes from marginal growth of bone. Perhaps the reason for this is that membrane appears to be a natural deterrent to otosclerosis. This is clinically observed when large mounds of otosclerosis are seen to build up along the margin of the window before the bone moves across the annular ligament and invades the footplate. The invading bone seems to have a hesitancy to enter, or cross, a ligamentous barrier. Again, once the footplate is involved, the otosclerosis seems to move around the edge of the footplate before it attempts to cross the ligament again to invade the surrounding labyrinthine capsule. Frequently, in massive otosclerotic involvement of the entire footplate and capsular area, one sees distinctly the indented area of the annular ligament indicating that it was slow to become involved. The membranous barrier to osteogenesis is a phenomena that helps protect the future mobility of the stapes even though protective judgment or lack of surgical precision may, in some instances, not allow the total removal of all otosclerosis around the oval window margin.

STEP NO. 8. *Return the tympanic membrane and skin flap back to their original positions and apply the routine external canal dressings.*

II. Posterior Partial Stapedectomy

PROCEDURE

Figure 2

Otosclerosis involving only the posterior rim of the oval window and the footplate of the stapes is rare, but does occur. Usually, however, what is thought to be an isolated posterior otosclerotic focus, on careful examination, is found to be related to definite anterior foot-

plate fixation by otosclerosis. As will be noted, the number of posterior segment operations is extremely small in this series (2) compared to the number of anterior segment operations performed (123). This suggests that the need for partial stapedectomy of the posterior segment is fairly small in the over-all picture.

The procedure of posterior partial stapedectomy is very similar to that of anterior partial stapedectomy.

STEP NO. 1. *Obtain good exposure.*

All of the factors mentioned above relating to the exposure to be obtained for anterior partial stapedectomy apply here. It should be emphasized that a careful analysis of the anterior footplate is necessary to exclude the possibility of pathologic fixation of the anterior area of the footplate. If questionable areas are found in the anterior footplate, or if good visualization cannot be obtained, the procedure would be immediately changed from that of partial stapedectomy with removal of the posterior segment to a partial stapedectomy with removal of the entire footplate. This will be described later. After the inspection of an anterior footplate which appears to be free of pathology, the microscope and the head are shifted so that the field of attention is directed to the posterior segment of the stapes. In order to properly carry out the posterior segmental removal, it is necessary to cut the tendon of the stapedius muscle. This is done with a sickle knife.

STEP NO. 2. *Transect the footplate.*

With a fine pick make a line of three to six holes in the footplate thus separating the pathologic area from the normal portion of the stapes. A wide margin of normal should be included in the pathologic segment. Cut between the pick holes with a chisel being careful not to penetrate deeply into the labyrinth. This line now transects the footplate and separates it into a pathologic posterior segment and a normal anterior segment.

STEP NO. 3. *Cut the posterior crus.*

The posterior crus should be cut near the neck with a small burr or a "whirlybird." It is usually desirable to remove a portion of the posterior crus to facilitate removal of the posterior segment. The

crus may be approached from either above or below or from its outer, or posterior surface, or from its inner, or obturator, surface.

STEP NO. 4. *Lift the pathologic segment out of the oval window*

Engage an extremely fine right angle, or 45 degree angle, pick in the line of transection and rotate it just under the pathologic segment of the footplate. Elevate the pathologic segment out of the window. Frequently, extremely firm fixation is present and the right angle footplate excavator mentioned above can be used to lift with safety the otosclerotic area out of the window.

STEP NO. 5. *Mobilize the anterior segment.*

STEP NO. 6. *Replace the mucous membrane over the oval window and seal the orifice with gelatin sponge or gelatin sheet (Gelfoam or Gelfilm), as is indicated.*

STEP NO. 7. *Return the tympanic membrane and skin flap to their original positions and apply the routine external canal dressings.*

III. Partial Stapedectomy with Removal of the Entire Footplate (Preservation of a Functional Stapes Without Substitution)

Again, the principles of, first, removal of pathology and, second, preservation of normal structures in a functional state without substitution are guides to our thinking. For example, if the footplate of the stapes is entirely invaded with otosclerosis, it must be entirely removed. If the footplate is diffusely involved in otosclerosis and the margin of normal and pathologic is vague, the entire footplate should be removed. If one complete edge of the footplate between the crura is definitely involved in otosclerosis, the entire footplate should be removed. In all these cases the object immediately becomes one of removal of all possible pathology, but, equally important, the object is to maintain a functional ossicular chain down to the oval window orifice. This means that the head, arch and one crus of the stapes must be retained throughout the procedure.

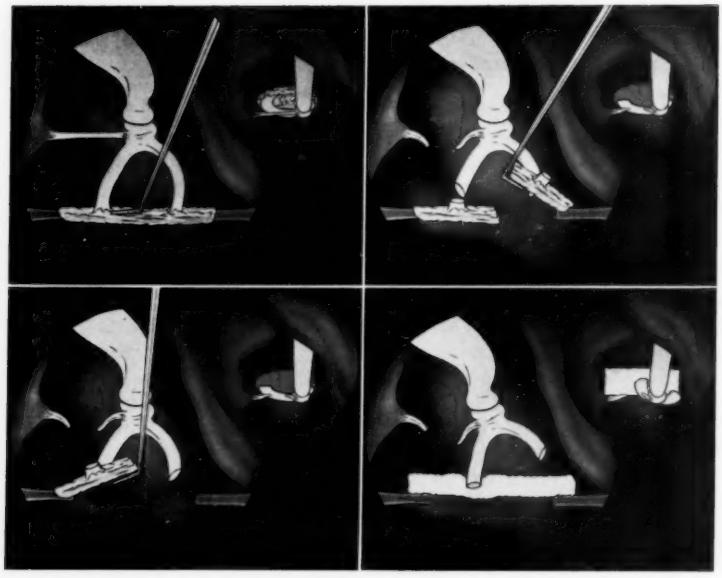

Fig. 3.—Total footplate removal.
(The sequence of these diagrams is: upper left, upper right, lower left, lower right.)

PROCEDURE

Figure 3

STEP NO. 1. *Obtain a good exposure.*

A wide exposure, as described above under partial stapedectomy for both anterior and posterior segmental removal, should be obtained.

During the inspection, determine the pathologic involvement, if any, of either crus. Also attempt to determine, if possible, the approximate area of the original otosclerotic invasion of the footplate. As much bone as possible should be removed in this area.

Due to the ligamental deterrent factor, once otosclerosis is on the footplate it has a tendency to remain for a long time confined to the

footplate area before crossing the ligament and invading again the labyrinthine capsule in a different area. As previously mentioned, this is demonstrated by the frequent finding of a footplate covered with otosclerosis with rolled edges at the margins indicating the reluctance of the otosclerosis to invade again the annular ligament. If the likely primary area of crossing of the original focus to the footplate can be determined, more complete removal of labyrinthine bone in this area is indicated.

STEP NO. 2. *Produce a lysis of the crura at the footplate.*

With a fine right angle, or 45 degree angle, pick, make perforations on each crus at the footplate level. With a whirlybird, complete the lysis of the crura at the footplate.

STEP NO. 3. *Lift the stapes aside.*

The stapes may be removed anteriorly, posteriorly, superiorly, or inferiorly to expose the footplate depending upon the anatomical positional requirements. It may be necessary to cut the stapedius tendon, or, occasionally, the incudostapedial joint may need to be partially, or completely, severed.

STEP NO. 4. *After good exposure of the footplate area, make an incision through the mucous membrane along the upper margin of the footplate with a footplate spatula knife.*

Elevate the mucous membrane with the knife spatula, or a chisel, toward the promontory. This mucous membrane is to be used later to cover the oval window area.

STEP NO. 5. *Transect the center of the footplate.*

With fine picks, make a line of transection across the center of the footplate. By rotating the picks gently like a burr, even thick bone can be perforated rapidly without excessive pressure. After making several perforations across the footplate, use a chisel to connect the perforations with cuts and thus complete the transection. If the bone is extremely hard, or extremely thick, one may desire to use a burr to thin the footplate as described by House.[12,13] A small dia-

mond, or cutting, burr may be used on a Wullstein hand piece or a Shea-Richards hand drill. After proper thinning, the footplate may then be transected.

STEP NO. 6. *Lift the pathologic footplate out of the oval window.*

Insert a right angle, or a 45 degree angle, footplate excavator through the line of perforation and immediately under the edge of the footplate. Elevate the anterior one-half of the footplate with its otosclerosis out of the window and remove it from the ear with forceps. Remove the posterior segment in the same manner.

STEP NO. 7. *Remove additional bone from the area of the original otosclerotic focus.*

With an excavator, remove bone from the margin of the fenestra in the area considered to be the original focus of otosclerosis.

STEP NO. 8. *Replace the mucous membrane as well as possible over the fenestral orifice and place a piece of Gelfoam measuring approximately 4 x 5 mm over the fenestra.*

Use a chisel to move this into position. Slide it into place inferiorly to hold the mucous membrane over the fenestra. Make a dent in the center of the Gelfoam with a chisel and place this area over the center of the window.

STEP NO. 9. *Place the end of the longest crus into the depression in the Gelfoam and rotate the arch and head of the stapes back into position.*

If it has been necessary to sever the incudostapedial joint in order to carry out some of the previous steps, one may still proceed to use the stapes. Ears have been re-entered by the author in which the stapes has been found to be present in good condition one-and-a-half years after this type of repositioning. There was no evidence of resorption.

STEP NO. 10. *Replace the tympanic membrane and skin flap to their original positions and apply routine external dressings.*

INDICATIONS FOR TOTAL STAPEDECTOMY

When the crura are being severed from the footplate if a fracture occurs which makes both of the crura too short to reach the oval window level, then the remainder of the stapes becomes non-functional and should be removed. There are also definite pathologic conditions which demand sacrifice of the entire stapes. If the otosclerotic bone has partially filled the niche and involves the crura, then the entire stapes must be forthrightly removed and replaced with either an artificial substance or a repositioned ossicle.

TABLE I

PARTIAL STAPEDECTOMY

	TOTAL NO. CASES	WITH ADEQUATE FOLLOWUP
Removal of anterior segment	123	115
Removal of posterior segment	2	2
Removal of footplate	16	14
Total	141	131

RESULTS

This paper presents 141 cases in which partial stapedectomy has been performed (Table I). These were done over a period of 17 months by the author. In order not to include figures of operations done too recently, the series was terminated February 1st, 1960. During this period of time, 834 operations on the stapes were performed and, therefore, it becomes apparent that partial stapedectomy was not the predominant operation. The reason for this is that until the last few months this operation was reserved for remobilization cases (those requiring secondary operations). It is now considered by the author to be the operation of choice as a primary procedure.

Since the anterior partial stapedectomy procedure was done in 123 of the 141 cases reported, these statistics will be predominantly discussed. The results of posterior segmental removal and total foot-

plate removal will be observed in the result tables presented in this article.

RESULTS IN ANTERIOR PARTIAL STAPEDECTOMY

The closure of the air bone gap is considered by many to be the only valid measurement of statistical evidence in surgery on the stapes. 123 anterior partial stapedectomies have been done during the past 17 months. 115 of these cases have been sufficiently followed post-operatively. The closure of the air bone gap in these ears makes an interesting study (Table II).

TABLE II

PARTIAL STAPEDECTOMY
CLOSURE OF THE AIR-BONE GAP

CASES		SUCCESS		
Cases which closed	115	Anterior removal	95	82.6%
the air-bone gap	2	Posterior removal	2	100 %
within 10 db or better	14	Footplate removal	9	65 %
Cases which closed	115	Anterior removal	88	76.5%
the air-bone gap	2	Posterior removal	2	100 %
within 5 db or better	14	Footplate removal	6	43 %
Cases which	115	Anterior removal	51	44.4%
overclosed the	2	Posterior removal	1	50 %
air-bone gap	14	Footplate removal	3	21.4%

Among the 115 ears in which anterior partial stapedectomy was done, 95, or 82.6%, reached a level of hearing within 10 decibels of the preoperative bone conduction, or better. This number of ears reached a near closure of the air bone gap.

Among the 115 ears operated, 88, or 76.5%, reached a level of hearing within 5 decibels of the preoperative bone conduction, or better. It is considered that these patients actually accomplished the so-called closure of the air bone gap since 5 decibels is within the margin of normal variation.

Of the 115 ears in which anterior partial stapedectomy was done, 51, or 44.4%, overclosed their air bone gap. In other words, the postoperative level of hearing was higher in the three speech frequencies than the preoperative bone conduction level in that ear.

The average preoperative air bone gap was 33.1 decibels.

The average postoperative air bone gap was 1.5 decibels. These cases experienced an average gain of 31.6 decibels.

These figures represent an extremely high over-all gain, but one must remember that included are those 44.4% which overclosed their air bone gap and these are weighed against those 23.5% which failed to reach a total closure.

CHANGES IN HEARING THRESHOLD

In the 115 cases followed in which anterior partial stapedectomy was performed, the average preoporative air conduction level was 50.3 decibels. The average postoperative air conduction level was 18.7 decibels. This makes an average air conduction gain of 31.6 decibels.

It should be pointed out that this series contained 11 cases in which it was predicted by bone conduction preoperatively that the hearing level could not possibly reach the 30 decibel level of adequacy due to cochlear deterioration.

If these are removed, a total of 103 ears were operated with good cochlear potential. 90 cases, or 87.4%, of this group reached the 30 decibel level of hearing, or better (Table III).

TABLE III

PARTIAL STAPEDECTOMY
CHANGES IN HEARING THRESHOLD

	CASES WITH COCHLEAR POTENTIAL OF 30 DB	CASES REACHING 30 DB OR BETTER	%
Ant. part. stapedectomy	103	90	87.4%
Post. part. stapedectomy	2	2	100 %
Footplate part. stapedectomy	13	9	69.2%

When speech thresholds and discrimination scores were correlated using the method of Walsh,[17] it is noted that due to cochlear loss 15 cases were considered in the improbable restoration category and were removed. When these were removed, 94 out of 100 cases, or 94%, were restored to a level of social adequacy (a social adequacy index of 50 or above).

Consideration will now be given to the general picture of those made better and those made worse. Out of 115 ears in which anterior partial stapedectomy was performed, 108, or 94%, were improved 10 decibels or more above their preoperative level. One ear in this series was made worse. The hearing regressed in this ear 14 decibels. It is noted that in this ear at the time of operation, the posterior crus was fractured near the footplate. Apparently this produced a separation of the ossicular chain resulting in a failure. A revision of this ear was done 6 weeks ago and a total stapedectomy with a plastic prosthesis has thus far produced an excellent gain in hearing.[13,15]

There were no serious postoperative complications in this series and no dead ears resulted.

REGRESSION

It must be strongly emphasized that this is only an early report of a new procedure. Although the results seem exceptionally good, long term results are not available. It is almost a certainty that there will be several regressions among these cases in the years to come because of the many factors so well known to all working in the field of otology. Nevertheless, it is believed that the number of regressions should be greatly reduced over the previous experience because of the following factors:

1. This operation has removed as much pathologic bone as is now possible and still maintained a functional natural ossicular chain. In many cases, complete extirpation of the focus is probable.

2. This operation has produced the formation of a wide membranous gap between the previously involved window margin and the new edge of the footplate. This membrane is a natural osteogenic deterrent and should discourage refixation by bony fusion.

Four ears out of the 115 anterior partial stapedectomy cases, or 3.4%, regressed over 5 decibels after their initial three weeks postoperative tests. Of these 4 cases, the amount of regression was 10 decibels, 8 decibels, 15 decibels, and 14 decibels respectively. In spite of the initial regressions, all of these cases except one have maintained very adequate hearing over six months and now seem to be stabilized. Contrariwise, there was a large number of ears in which the hearing improved significantly up to 20 decibels between the three weeks, three months, six months, and one year postoperative tests.

With the rapid advancement in otologic surgery during the past few years, one can predict with near surety that improvements in techniques will occur in the future. In performing a partial stapedectomy, one has not compromised the future beyond reasonable risk and in case of a long term regression more can be done in the same ear with the probable advantage of new advanced procedures.

SUMMARY

Procedures termed partial stapedectomy have been presented for the restoration of hearing in the otosclerotic ear. An attempt is made in these procedures to:

1. Remove the diseased portion of the stapes; and
2. Preserve all normal structures in a functional state.

The results reported here seem to recommend this segmental removal of the stapes as theoretically sound and functionally effective. Further investigation and clinical trial is encouraged to develop more completely this concept of surgery on the stapes.

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XLVII

STAPEDECTOMY

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To aid us in assessing new surgical techniques for otosclerosis we have performed a series of animal experiments. Ideally, a new surgical method should be performed first on animals. If it cannot be evaluated logically on animals it may be permissible to try it on humans if it is based on sound physiological principles and, when viewed in the light of medical knowledge, it has a high index of predictability. The chart in Figure 1 shows that usually we have succeeded in preceding or paralleling new operations for otosclerosis with appropriate animal experiments.

1. *Stapes Mobilization.* Experimental fracture of the stapes in rabbits[1] and cats[2,3] has resulted in rapid healing by new bone formation (Fig. 2A). The human stapes appears to respond similarly to trauma, accounting for the high incidence of reankylosis following stapes mobilization.

2. *Mobilization with Crural Substitution.* We first used metal implants in humans when attempts to mobilize resulted in crural fracture with loss of "columella" effect. These implants of tantalum or steel wire were so designed that one end was in contact with the footplate and the other hooked to the long process of the incus. An animal experiment showed that tantalum was well tolerated in the middle and inner ears for short periods of time (five months)[4] (Fig.

The animal research was supported entirely by a grant from the Central Bureau of Research of the American Otological Society.

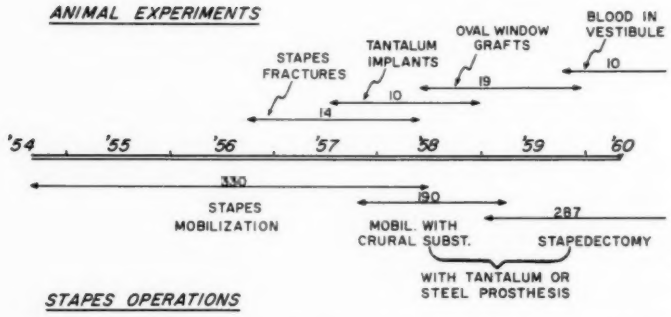

Fig. 1.—This chart shows the chronological relationship of animal experiments to stapes procedures for otosclerosis.

2B). It was also noted that small fistulas in the footplate, or at its margins, were healed by a thin muco-endosteal membrane.

A surgical procedure, based in part on these experimental findings, consisted of the following steps: removal of the head, neck and crura of the stapes; mobilization of the thin or nearly normal portion of the footplate with fine chisels; and, replacement of the crura with a prosthesis of sufficient length to depress the mobilized portion of the footplate slightly from contact with the surrounding bone or annular ligament or both.

Whereas the early success rate was higher than with previous forms of stapes surgery, and the metal implants appeared to be well tolerated, there were several factors which led to discontinuance of this procedure.

a) There were considerable technical difficulties in the execution of the operation.

b) The footplate manipulations were more extensive so there was a higher incidence of postoperative vertigo and high tone deafness. It was coincidentally discovered in animals that excessive footplate manipulations resulted in damage to the organ of Corti in the upper basal turn[5] (Fig. 3).

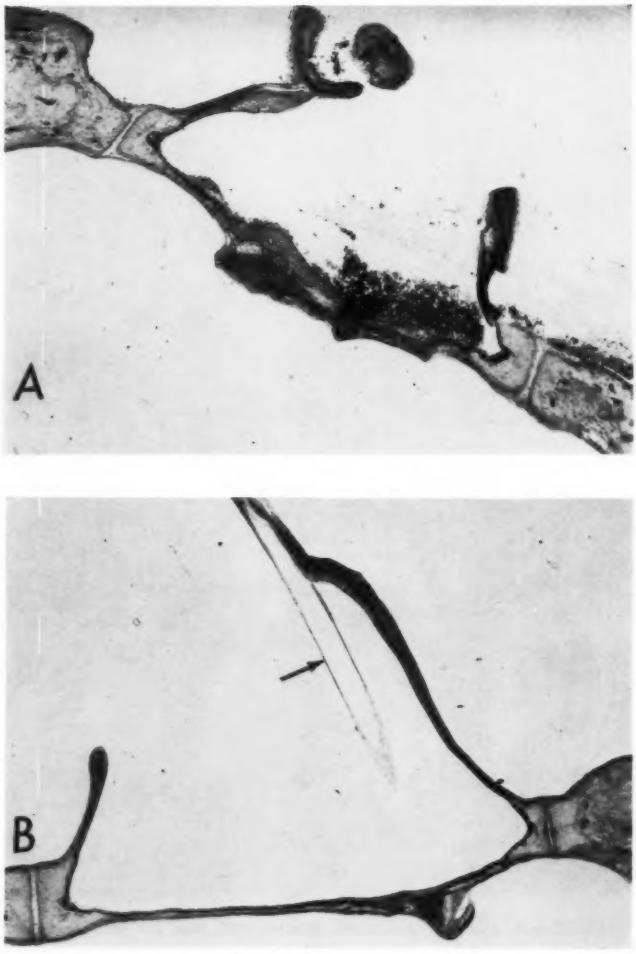

Fig. 2.—A. The comminuted fracture of the footplate of the cat resulted in complete bony healing eight months after injury. B. The arrow indicates the mucosal sheath which completely covered a tantalum wire in the middle ear of the cat 87 days after operation.

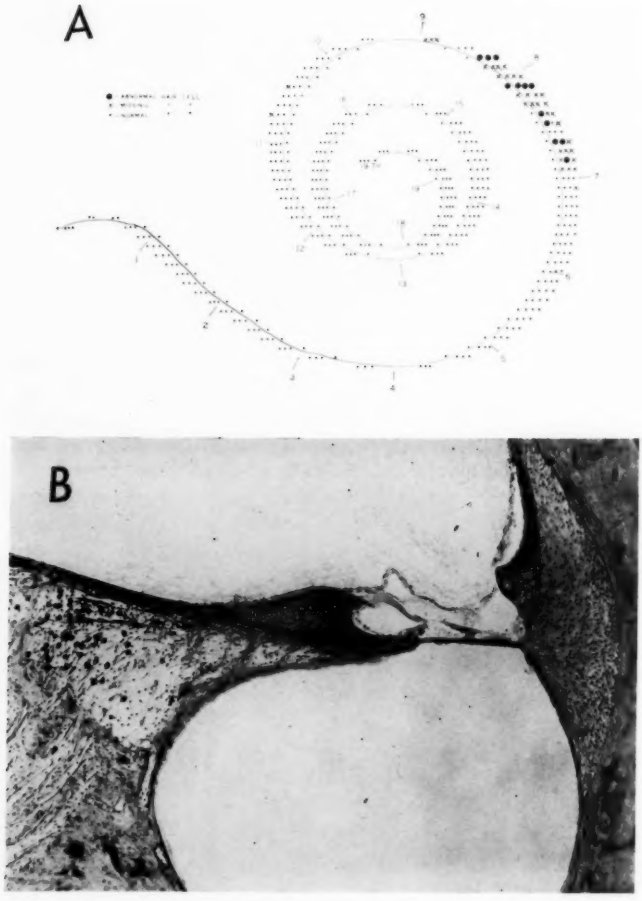

Fig. 3.—A. Cochlear reconstructions showing hair cell loss in the seven to nine mm area resulting from fracture dislocation of the anterior two-thirds of the footplate. B. From the eight mm region showing rupture and collapse of Reissner's membrane, extensive damage to the organ of Corti, and secondary degeneration of the spiral ganglion.

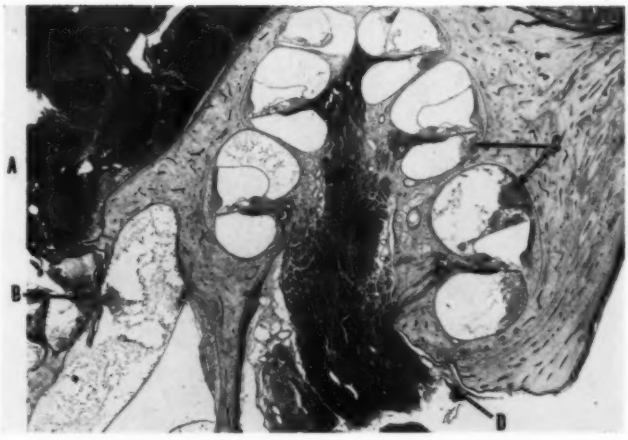

Fig. 4.—Inward displacement of the anterior half of the footplate resulted in a permanent oval window fistula (B). Three months after surgery the animal developed suppurative otitis media (A), labyrinthitis (C), and meningitis (D). The gap in this footplate obviously was too large to heal spontaneously.

c) There were 2 of 24 animals with experimentally produced footplate fractures which developed fistulas followed by suppurative labyrinthitis and meningitis, therefore, it appeared that this particular operation was hazardous (Fig. 4).

3. *Stapedectomy.* Shea[6] had already shown on humans that the stapes could be removed and replaced by a vein graft and polyethylene tube without damage to the inner ear, with excellent functional results, so that our interests were directed toward the principle of stapes substitution.

An experiment was performed on cats in which the incus and stapes were removed and soft tissue grafts introduced into the oval window niche (Figs. 5 to 7). One of the difficulties encountered was that the outflowing perilymph tended to displace the grafts from the margins of the oval windows. In a current experiment, in which we are studying the effect of blood in the vestibule, this problem has

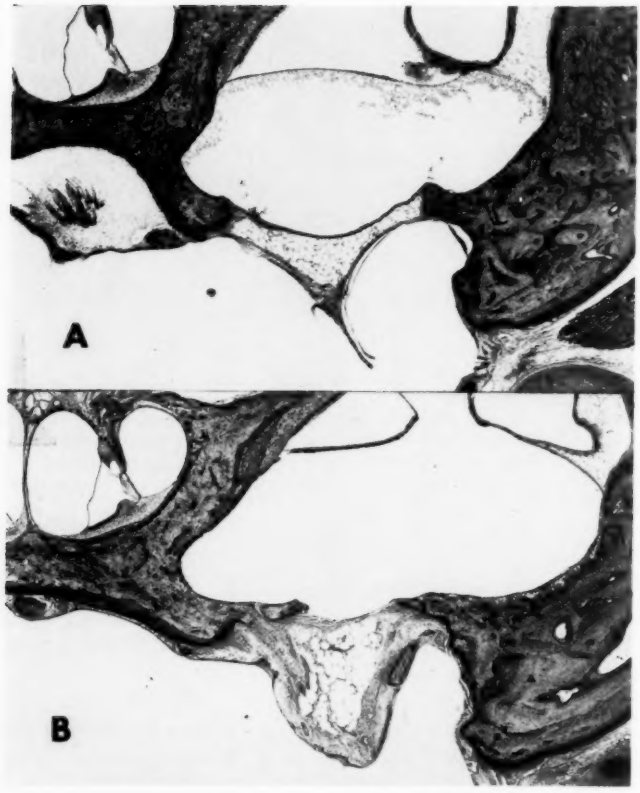

Fig. 5.—A. Stapedectomy and adipose tissue graft in the cat. Sacrificed three months after operation. B. Stapedectomy and adipose tissue graft. Sacrificed 13 weeks after operation.

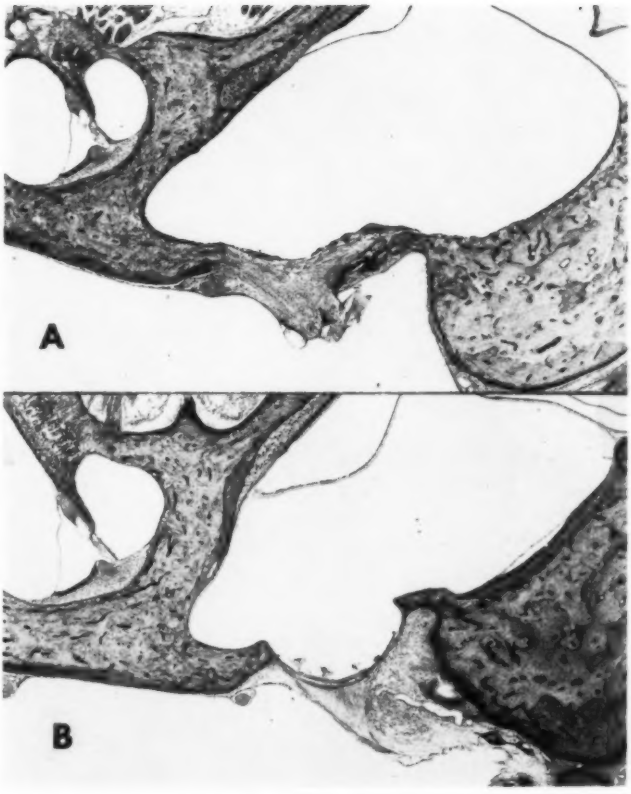

Fig. 6.—A. Stapedectomy and connective tissue graft in the oval window of the cat. Sacrificed two and one-half months after operation. B. Stapedectomy and connective tissue graft in the cat. Sacrificed two and one-half months after operation.

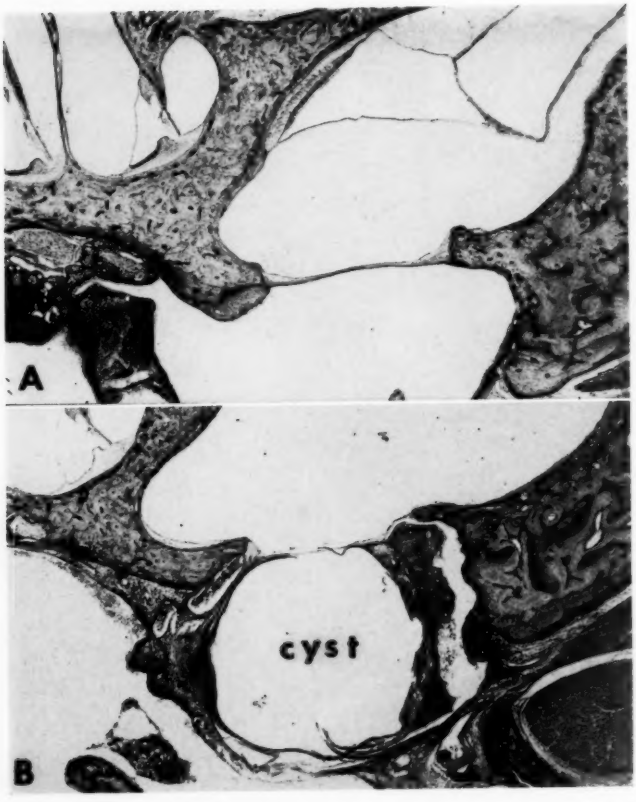

Fig. 7.—A. Stapedectomy with mucous membrane graft in the cat. Sacrificed nine weeks after surgery. B. Stapedectomy and skin graft to the oval window in the cat. Sacrificed four and one-half months after surgery. A large epidermoid cyst has formed.

been avoided by prior removal of cerebrospinal fluid which reduces perilymphatic pressure.

The animals were sacrificed two to four months after implantation of the grafts, following which the temporal bones were sectioned in the usual way. A detailed description of the experiment will appear elsewhere.[7] The study showed that grafts of mucosa, connective tissue, and fat persisted as viable membranes in the oval window. An epithelial lining formed on both the vestibular and tympanic surfaces of the grafts. There was no evidence of proliferation or atrophy, and the various tissues retained their identity. In those ears in which the position of the graft was properly maintained, there was no inner ear damage. Dislocation of a small part of the graft occurred in several ears and resulted in fibrous healing without inner ear damage. Dislocation of greater parts of the grafts resulted in varying degrees of inner ear damage, which varied from mild fibrous proliferation in the vestibule to total destruction of the cochlear and vestibular sense organs.

We reasoned that either loose areolar connective tissue or adipose tissue would best meet our requirements for a graft. We want tissue which is easy to acquire and which will remain freely movable in the oval window. Our latest method for making the graft prosthesis is shown in Figure 8.

We have performed stapedectomy on 287 patients on whom auditory tests are available (average interval after operation is four months). The prostheses consisted of either tantalum or steel wire. Postauricular subcutaneous connective tissue was used in 167, adipose tissue from the ear lobe in 106, vein in 2, and gelfoam in 12.

Our results have been evaluated by averaging 500, 1000 and 2000 cps, and comparing the postoperative air conduction thresholds with the preoperative bone conduction thresholds (Table I).

TABLE I

RESULTS OF 287 STAPEDECTOMIES

Bone-air gap of 5 db or less	161	(56.8%)
Bone-air gap of 10 db or less	215	(74.9%)
Bone-air gap of 15 db or less	242	(84.3%)

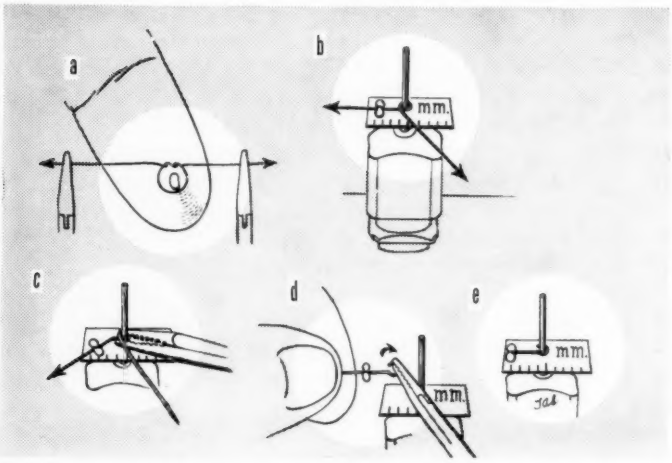

Fig. 8.—Method for making the graft-prosthesis: A. A piece of soft tissue (e.g. ear lobe fat) is knotted to a piece of 36 gauge tantalum or steel wire. B. The incus ring is made by looping the wire around the post of the die. C. The shaft of the prosthesis is bent where it meets the incus ring. D. The wire of the incus ring is cut where it meets the shaft and the incus ring is "opened." E. The wire at the opposite end of the prosthesis is cut close to the knot. The finished prosthesis measures about 5 mm in length and the tissue should measure about 2 x 3 mm with the long axis parallel to the plane of the ring.

Significant high tone sensorineural losses (20 db or more for 4000 cps) were found in 50 (17.4%) of operated ears. Of this group there were five with hearing losses for 2000 cps of sufficient magnitude to effect speech discrimination. In four patients original hearing gains have been lost due to a recurrence of the conductive deafness. Two of these who have been reoperated were found to have extensive recurrence of bone growth in the oval window. Delayed sensorineural degeneration occurred in seven (2.4%). The functional result was not dependent upon the type of tissue (connective tissue or fat) or the type of metal (tantalum or steel).

4. *Delayed Cochlear Degeneration.* Delayed cochlear degeneration occurred in seven (2.4%) of our patients. Usually the hearing

loss occurred suddenly (over a period of several hours), about one to three weeks after surgery, after an initial hearing gain. Usually it was not accompanied by vertigo, although several patients had mild transient unsteadiness. The loss was characterized by a moderately severe deficit for pure tone thresholds and a severe loss in speech discrimination so that the ear became functionally useless.

Although the exact reason for the delay is a mystery, we definitely can relate our cases to inner ear trauma, occurring at the stapedectomy operation or at previous stapes operations (Table II). We believe the incidence of cochlear degeneration can be reduced by avoiding labyrinthine injury:

TABLE II

SEVERE SENSORINEURAL LOSSES

CASE	AGE	DELAY	REMARKS
1	45	1 mo.	Traumatic FP removal c vertigo
2	45	5 mos.	ONE previous operation c vertigo
3	64	2 wks.	ONE previous operation c vertigo
4	44	?	Nothing unusual
5	20	2 wks.	TWO previous operations c vertigo
6	38	1 mo.	TWO previous operations c vertigo
7	62	?	Postoperative hematotympanum

a) Avoid stapedectomy on ears on which there is a history of previous stapes surgery accompanied by excessive vertigo.

b) Discontinue operative manipulations which cause dizziness. (All but one of our patients with delayed cochlear degeneration experienced vertigo during the stapedectomy procedure.)

c) Remove the stapes piecemeal, beginning with a small perforation so as to avoid excessive displacement of labyrinthine fluids.

d) When removing the footplate do not introduce instruments beyond those necessary to engage the fragments.

e) Do not attempt to remove either large or small fragments of footplate which have receded into the vestibule; allow them to remain and superimpose the graft in the usual manner.

f) Avoid excessive manipulations such as "pumping" the graft-prosthesis in the oval window to test its action.

SUMMARY

The results with stapedectomy are so good that in spite of the incidence of delayed cochlear degeneration, the operation appears superior to other procedures for otosclerosis. At this time we believe there is no functional difference between various implants being used to replace the stapes, so the choice of technique is one of individual preference. A factor of great importance is that of surgical skill. The skilled surgeon, following strict rules of procedure to avoid labyrinthine trauma, will experience fewer complications than the occasional operator.

Of 287 stapedectomies in which a tissue-metal implant was used, bone-air gap of 10 db or less was acquired in 74.9%. Delayed cochlear degeneration occurred in 2.4%.

On the basis of earlier experiences, we predict that bony reclosure of the oval window will occur eventually in ears in which there is extensive or active otosclerotic disease. On the other hand, we believe that the operation may be permanently successful for ears with small inactive otosclerotic lesions.

HENRY FORD HOSPITAL

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XLVIII

ACCELERATION AS A MEANS OF DETERMINING THE SENSITIVITY OF THE COMPONENTS OF THE NON-AUDITORY MEMBRANOUS LABYRINTH

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AND

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Although it is readily possible to stimulate the organ of balance in the head by various means(caloric, electrical, rotation), the most physiological of these consists of change in magnitude or direction of velocity; this applies whether the motion is linear or angular. At the Vestibular Research Clinic at St. Michael's Hospital in Toronto, the responses of normal and diseased labyrinths to controlled accelerations are being compared by a device, which enables humans to be exposed to various magnitudes and types of motion. A description of this procedure together with recordings of various vestibular responses will be given.

Disorders of equilibrium due to lesions involving the non-auditory membranous labyrinth in the head may result in sensations of rotation, of tilting without rotation, or combinations of each. Although the patient may describe these, and indeed other illusions of movement (including blurring of vision, etc.) under the title of dizziness, the specific origin of the lesion as far as the separate components of the vestibular apparatus is concerned often presents a considerable challenge to the otologist. The main reason for this last statement stems from the fact that the need exists for a practical means to enable stimulation not only of the otoliths as distinct from the semi-

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circular canals but also for stimulation of the separate sensory vestibular receptors which are specialized for the perception of angular movements in different planes of space. Although it has been well established by such investigators as Flourens, Tait, McNally and others, that the semicircular canals oriented closest to the plane of rotation are the ones in which the greatest flow of endolymph occurs during rotation in any one plane of space, experimental evidence already exists (Spiegel, Johnson et al.) to show that the greatest displacement of endolymph may occur in a semicircular canal (or pair of diagonally opposite canals) which is not anywhere close to the plane of rotation of either the head or the trunk. This undoubtedly could account for the rather surprising illusion of vertigo which patients describe as occurring when certain types of even small head movements initiate nystagmus. It is the object of this paper to explain the significance of the flow of endolymph which may result from head movements, when one or more of the canals is simultaneously stimulated by angular movements of the trunk in another plane of space. Furthermore, a description given of our clinical research program which, it is felt, enables a practical means of reproducing all the various types of illusions which are possible due to stimulation of the various semicircular canals either singly or in pairs. Thus, the symptoms of the patient can be more accurately correlated with the specific semicircular canal or canals involved, and by using rotation as the vestibular stimulus in the clinic, information can be obtained to facilitate localization of the site of the lesion as far as the components of the non-auditory end-organ are concerned. Furthermore, for reasons given below, we have evidence for believing that it is also possible selectively to determine the integrity of the otoliths as distinct from the semicircular canals.

PROCEDURE AND RESULTS

In order to understand the physiologic basis of the procedure recently instigated in our clinic, it is first necessary to clarify the resulting movement of endolymph relative to the walls of the semicircular canal concerned when the patient's trunk is rotated about one axis, while his head is rotated about an axis in another plane of space. This can be most readily appreciated by observing the flow of fluid contained in a transparent model of the semicircular canals and utricle. This we have done by means of moving pictures. A detailed mathematical analysis of the nature of such simultaneous

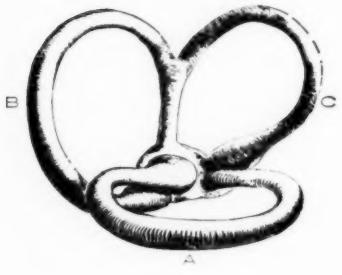

Figure 1

angular movements has been described by Meda from the point of view of the physicist, while the general autonomic effects of such complex accelerations have been described by Johnson et al., Spiegel and Schubert.

Examination of fluid flow relative to the walls of the semicircular canals shows that (Fig. 1) when one of the canals (Canal A) is in the plane of rotation and simultaneous rotation of the system simultaneously occurs in the plant of another canal (Canal B), the greatest displacement of fluid takes place in the third canal (Canal C) which is not in the plane of rotation.

In regard to subjective sensations, it is well known that when the normal patient is rotated about a vertical axis, shortly after the onset of a constant rate of rotation, no sensation of this movement occurs provided the head remains fixed relative to the trunk (at this time the endolymph in the semicircular canals is stationary relative to the membranous walls). It is also well known that an abrupt deacceleration causes a sensation (with nystagmus) of spinning in the opposite direction. It is possibly less well known that should a forward nodding of the head occur immediately either during rotation or after the stop, an illusion of rotation (with nystagmus in the appropriate plane) occurs diagonally downward. This situation of course has its threshold of excitation and can be produced even when the fluid of the canal in which the basic or initial rotation is occurring be stationary (relative to the walls of the canals), or else is moving. The former effect may occur on constant rate of rotation of the body

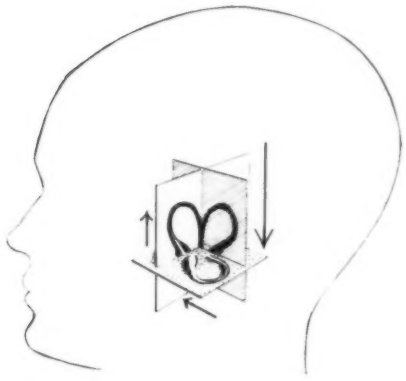

Fig. 2.—Vectorial representation of endolymph. The arrows represent magnitude and direction of fluid flow.

with superimposed head movement. The latter effect occurs at the beginning or cessation of body rotation with superimposed head movement also in another plane of space. The former resulting angular acceleration has been called by Meda the Coriolis and the latter the Purkinje phenomenon. It should be pointed out that the subthreshold rates of acceleration for excitation of any two canals when determined singly by angular acceleration in the plane of each canal alone may be combined to produce a resultant which is above the threshold of excitation for the third remaining canal. This situation can be represented by means of vectors (Fig. 2) which represents magnitude and direction of fluid movement in the various canals.

The rationale for selective stimulation of the various semicircular canals can best be understood by reference to Figure 3.

Suppose the patient is seated and rotating in an anti-clockwise direction around a vertical axis passing through the center of the head. A constant rate of rotation is attained and the endolymph is stationary relative to the walls of the canals. The head is now rotated in the plane of the right superior and left inferior canals. This combination of angular movements in two orthogonal planes of space causes a relatively large resulting angular acceleration in the remaining orthog-

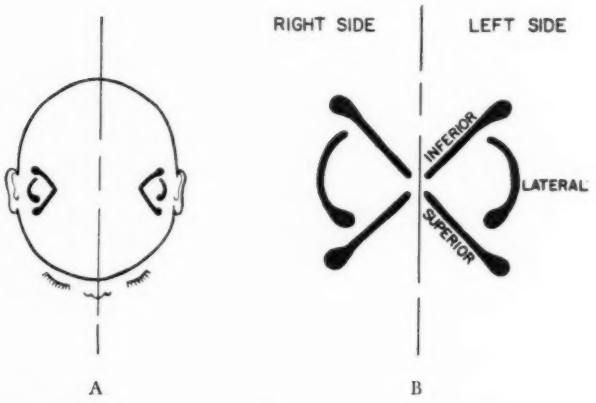

Figure 3

onal plane, so that the movement of endolymph is greater in the semicircular canals lying in the remaining orthogonal plane, namely the left superior and right inferior canals. Furthermore, the resulting vertigo is also in the plane in which the right superior and left inferior canals lie so that the patient experiences a sensation of rotating downward, forward, and to the left, and with corresponding nystagmus.

Now, considering one canal at a time, this sensation is undoubtedly the same as occurs when the left superior canal is maximally stimulated (ampullar leading in the direction of movement). Thus by using a combination of rotation in two planes of space at right angles to each other, there occurs a relatively large endolymph flow in the third remaining plane and by remembering that the lateral canals are stimulated maximally by an ampulla-trailing motion, while the vertical canals are maximally stimulated by an ampulla-leading motion, it is possible to determine which semicircular canal is maximally stimulated by the simultaneous application of two angular motions of the head in the planes which are at right angles to each other. These effects are summarized in Table I.

Thus by proper positioning of the head during constant rate of rotation of the trunk about a vertical axis, subsequent head movement

TABLE I

ROTATION	CANALS IN PLANE OF BODY ROTATION	*Maximal Stimulation*	CANALS IN PLANE OF SUPERIMPOSED HEAD MOTION	*Maximal Stimulation*	CANAL MAXIMALLY STIMULATED
C. C.	Laterals	Left Lateral	Right Superior and Left Inferior	Right Superior	Left Superior
C. W.	Laterals	Right Lateral	Left Superior and Right Inferior	Left Superior	Right Superior
C. C.	Laterals	Left Lateral	Left Superior and Left Inferior	Left Superior	Left Inferior
C. W.	Laterals	Right Lateral	Right Superior and Left Inferior	Right Superior	Right Inferior
C. C.	Right Superior and Left Inferior	Right Superior	Left Superior and Right Inferior	Left Superior	Left Lateral
C. W.	Left Superior and Right Inferior	Right Inferior	Right Superior and Left Inferior	Left Inferior	Right Lateral

NOTE: C. C.: Counter clockwise
C. W.: Clockwise

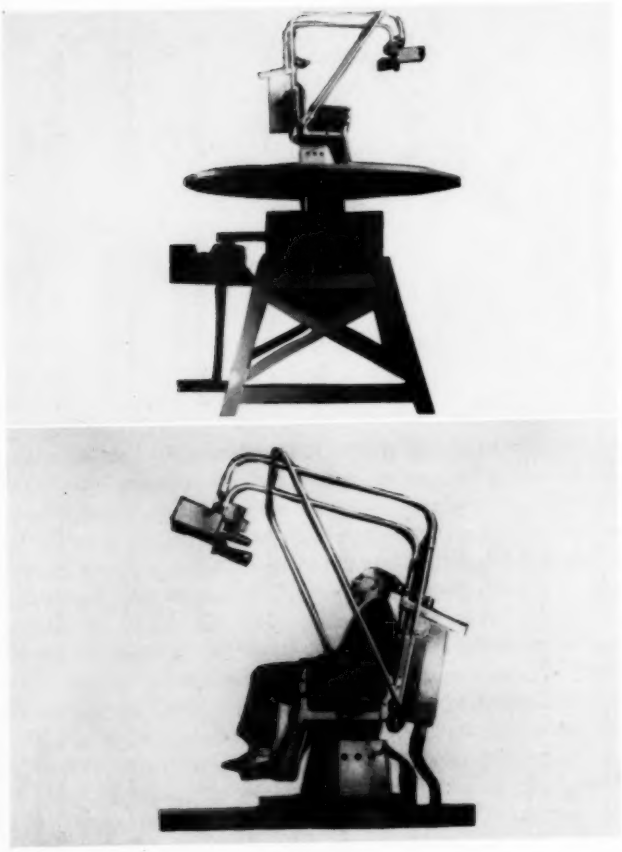

Figure 4

in another orthogonal plane makes it possible to selectively stimulate any of the six canals. To enable this an appropriate device has been devised as illustrated in Figure 4.

It essentially consists of a variable speed platform on which is mounted a variable position chair, provided with a means for controlled head movements. By first tilting the patient's head into the appropriate position, specific opposite pairs of canals can be accurately placed in the plane of rotation prior to superimposing any head movement in another plane. This initial positioning of the head (e.g. lateral canals in plane of body rotation) can be readily accomplished by using external anatomical references. When, for example, a constant angular rotation is maintained in the plane of the lateral canals, tilting (nodding) the head forward or backward changes this angle from zero (lateral canal 30° with the horizontal plane) to some plus or minus value in degrees. The vector relationships of fluid movement in all canals is thereby altered so that the one in which the greatest flow of endolymph occurs is the one in which plane the resulting nystagmus is produced and is also the plane in which the subjective sensation of rotation occurs. Since the nystagmus is the more readily measurable sensory response, a means is incorporated to allow a suitable recording. A nystagmogram is enabled by a photo-electric method (Sullivan, Johnson and Smith), by recording corneo-retinal potentials or by a closed circuit television system connected to slip-rings enabling a magnified and clear image of the patient's eye to be produced for visual (or photographic) inspection on a stationary viewing screen.

This last method has the additional advantages of reproducing rotatory eye movements about the anteroposterior diameter of the eyeball and also of eye deviations due to utricular or saccular stimulation.

The head support has a linear backward and forward motion accomplished by a hydraulic cylinder linkage and powered by a hydraulic package contained in the chair mounting housing. Speed of head movement is varied by the flow control valves supplying the cylinder. The length of the stroke and therefore the arc of head movement are also variable. The frequency of operation is determined by an electrical timer at the console which operates a solenoid valve for the hydraulic cylinder.

The rotating platform is attached to a large central spindle which runs on precision tapered roller bearings. The spindle is hollow and has slip-rings at the lower end both for power supply and for distortion-free recordings of electrophysiologic responses.

The main speed drive consists of a constant speed A.C. motor connected to an eddycurrent clutch. Maximum speed of the table is 50 RPM and it can be accelerated to this speed or any other preset speed from 0 to 50 RPM in between 8 and 100 seconds. Braking of the table is effected by an eddycurrent brake which operates on the same principle as the driver.

The chair is also adjustable for fixation at any position along the ten foot diameter of the platform. Although angular velocity is independent of the radius, this arrangement enables application of different linear acceleration to be imposed on the otoliths. Thus, production of the "oculogravic illusion" so well described by Graybiel is available. With the patient's head fixed relative to the trunk, rotation of the body around a vertical axis exposes the otoliths to a combination of linear forces, namely the outward centrifugal force and the downward pull of gravity. The resultant is a relatively large linear acceleration in another plane and this produces a tilting sensation (oculogravic illusion) which occurs in the direction of the resultant force and which is proportional to the radius and speed of rotation. Should it be established, and we have evidence for this, that the otoliths of the utricle are maximally stimulated by linear acceleration in one plane, while those of the saccule by linear acceleration in another plane, then by proper orientation of the head, the sensitivity (threshold) of the separate maculae can be established as can the threshold of the various semicircular canals also be determined. It should be pointed out that any attempt to stimulate the otoliths alone, whether to determine their threshold of excitation or to induce more violent responses, must be induced by completely avoiding exposure to angular accelerations below that considered to represent the threshold accelerations of the semicircular canals. This minimal value is considered as being one degree per second.[2]

The specific acceleration of the endolymph to which resulting movement is given can be calculated as equal to the sum of the centripetal acceleration, the acceleration of the additional motion and twice the vector product of the angular velocity by the added velocity.

Since it is more practical to measure accurately the constant rate at which a subject is being rotated and to superimpose a known controlled head movement, we have decided to use this procedure in an attempt to determine an index of Coriolis acceleration for semicircular canal threshold of excitation. We thus maintain a constant head motion and by simultaneous application of angular velocity of different values, produce variations in resulting Coriolis acceleration causing different magnitudes of nystagmus and sensations of vertigo. The threshold can obviously be determined from these values in that there must therefore be a threshold angular velocity below which the resulting Coriolis acceleration is non-effective. In our test we have found a considerable range for the normal subject varying from 24°/sec to five times this value. These magnitudes are of course dependent upon the rate and angle of head movement which must be maintained constant during the test.

One may well ask, why not express the results in absolute terms of Coriolis accelerations. Strictly speaking this is impossible since it can only be done for one part of a semicircular canal (or point in the endolymph) at a time. This is because different parts of the canal are situated at different distances from the axis on which the head rotates. However, a quantitative expression can be obtained by multiplying the threshold angular velocity of the trunk by a constant, the latter representing the rate of head movement and the arc through which it moves. Five patients with complete non-functional labyrinths unilaterally (three due to end-organ pathology and two the result of labyrinthectomy) failed to demonstrate the oculogyral illusion described above when rotated in one direction only in the sitting position around a vertical axis passing through the center of the head and with superimposed nodding of the head. The direction in which rotation of the trunk (clockwise or anti-clockwise) did or did not show this effect depended upon which side of the head the non-functional labyrinth was located. Thus the three patients with no end-organ on the right side did not experience the oculogyral illusion when the trunk was rotated clockwise but did demonstrate the effect when rotated in the opposite direction. The two patients without end-organs on the left side showed the effects when rotated clockwise, but none could be produced when rotated anti-clockwise. The explanation of this is apparently based on direction of maximal stimulation for endolymph flow in the lateral canals.

SUMMARY

Although it is possible to stimulate the organ of balance in the head by various means, the most physiologic of these consists of change in magnitude or direction of velocity; this applies whether the motion is linear or angular. At the Vestibular Research Clinic at St. Michael's Hospital in Toronto, the responses of normal and diseased labyrinths to controlled accelerations are being compared by a device which enables exposure to various magnitudes and types of motion thereby making it possible selectively to stimulate otoliths and semicircular canals. In regard to the semicircular canals, the simultaneous exposure of the head to angular motion in any two planes of space at right angles to each other, produces a resultant acceleration in the third remaining orthogonal plane. By proper orientation of the head under these conditions, it is possible to determine the threshold of excitation to angular motion of the various semicircular canals individually. Furthermore, by proper positioning of the patient with the head fixed relative to the trunk, rotation of the body at various speeds enables a determination of the threshold of excitation of the otoliths. In both of these arrangements, both subjective and objective vestibular responses can be accurately recorded during rotation, the latter by means of closed circuit television which enables all types of eye responses to be recorded with relative ease. The application of these procedures to the study of diseased labyrinths is apparent.

174 St. George St.

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XLIX

LOCALIZATION DIFFICULTY IN MONAURALLY IMPAIRED LISTENERS

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Clinically, deterioration in the ability to localize sound is generally accepted as a component of unilateral hearing impairment. In the clinical situation, one is impressed by apparent variations in the actual amount of difficulty patients describe. Some report difficulty locating sounds within their homes; some are unable to identify the position of game while hunting; some experience confusion in locating and identifying an individual speaker within a group. Other patients, however, report no difficulty even though they have significant monaural impairments. While the presence of a unilateral loss is most often first recognized because of difficulties in locating sounds or hearing speech on the impaired side, it is not an infrequent experience to see a patient whose significant unilateral impairment remained unrecognized for many years. It may have been accidentally discovered during a school hearing survey or when a telephone was placed to the ear not habitually used for that purpose. Frequently, these patients did not believe that localization of a sound was a problem to them.

These variable patient's reports of localization difficulty led us to question the nature of this problem and consequently to propose a study which we hoped would elucidate the following questions:

1) What amount of difficulty in localizing sound is normal?

2) How much difficulty can we assume a unilateral loss will impose upon its listener?

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3) If variations in localization difficulty do exist, how great are they, and to what factors are they related?

4) Do persons with congenital unilateral auditory impairment localize sound better than those who had had normal binaural function and then acquired unilateral loss?

5) Does localization ability improve with time; specifically, is there a learning factor operative to improve this ability after it has become impaired?

SUBJECTS

A total of 91 subjects were tested, of whom 40 represented normal hearing listeners, and 51 represented unilaterally impaired listeners. In the normal hearing population, 10 subjects were children, 10 were adult females, 10 were adult males, and 10 were adults with varying degrees of isolated high frequency hearing loss above 3000 cps. The mean age of the normal hearing population was 28.4 years, and in those subjects with high frequency loss the mean loss at 4000 and 8000 cps was 59 db.

In the population with monaural hearing impairment, 22 subjects were male, 29 were female, and of these, 8 were children ten years of age or less. While some subjects had a mild hearing loss in the better ear, all subjects met the two criteria for acceptance of 1) normal speech hearing function in the better ear (PB discrimination of 90% or more) and 2) at least 30 db greater loss in the poor ear as compared to the better one. Of the 51 impaired subjects, 33 had completely normal better ears, and 18 had some degree of high frequency loss, the mean of which was 57.2 db at 4000-8000 cps. The mean pure tone threshold level at 500-2000 cps for the better ear was 1.2 db, as compared to 63 db for the poorer ear, with the mean db difference between the better and poorer ears equal to 61.8 db. The mean age of the unilaterally impaired subjects was 38 years; the mean duration of the loss was 9 years.

ROOM AND EQUIPMENT

This study was conducted in the Audiology and Speech Clinic of the University of California Medical Center, San Francisco, California. While this room is not sound-proof, its ceiling is treated with acoustic

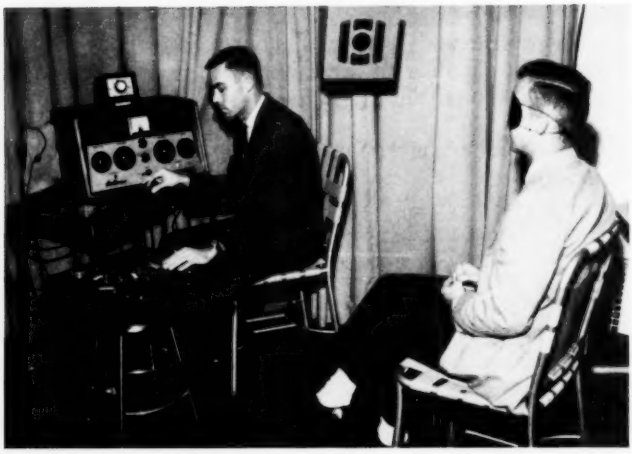


Fig. 1.—Indicates position of examiner, blindfolded subject, and rotating speaker from which stimulus was presented.

tile and all walls are draped lined to reduce reverberation and maintain reasonable acoustic conditions. The stimulus signal was taped on an Ampex Model 600 tape recorder, which was connected to a Beltone 15A Audiometer from which both the signal level and complex noise levels were controlled. The stimulus signal was presented from a Jensen Speaker, fixed to a boom held four feet from the floor, which rotated circularly in a four foot radius, and which was attached to and controlled by a CRR Rotor, Model AR-1. Complex background noise was introduced through two Jensen Concrete Speakers placed laterally to the side of the subject who was seated directly under the center of the rotating boom.

PROCEDURE

Listeners were blindfolded, instructed to maintain their heads in a fixed position and to point, as exactly as possible, to the apparent source of a tape recorded sentence "Will you please point to me now." This sentence, delivered at 30 db above the better ear speech reception threshold, was presented from the loudspeaker which rotated to eight

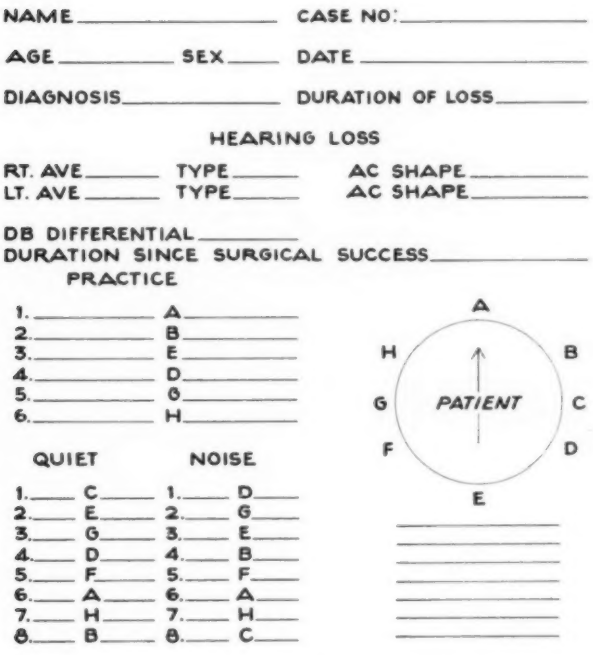

NAME _____ CASE NO: _____
AGE _____ SEX ____ DATE _____
DIAGNOSIS _____ DURATION OF LOSS _____
HEARING LOSS
RT. AVE _____ TYPE _____ AC SHAPE _____
LT. AVE _____ TYPE _____ AC SHAPE _____
DB DIFFERENTIAL _____
DURATION SINCE SURGICAL SUCCESS _____
PRACTICE
1. _____ A _____
2. _____ B _____
3. _____ E _____
4. _____ D _____
5. _____ G _____
6. _____ H _____
QUIET NOISE
1. ____ C ____ 1. ____ D ____
2. ____ E ____ 2. ____ G ____
3. ____ G ____ 3. ____ E ____
4. ____ D ____ 4. ____ B ____
5. ____ F ____ 5. ____ F ____
6. ____ A ____ 6. ____ A ____
7. ____ H ____ 7. ____ H ____
8. ____ B ____ 8. ____ C ____
A
H
B
G
PATIENT
C
F
D
E

Fig. 2.—Form utilized to summarize information and record localization judgements.

positions in a circle about the subject's head. Each subject was given a short practice session of standard length, following which he was to localize the eight positions under the two conditions of the test, once with the room quiet, and again with a background of equal level complex noise. Test conditions were alternated, with half of the subjects tested first in quiet, the other half tested first in noise. Scores were obtained to indicate 1) the number of errors made, and 2) the size of the error made. Each error occurring received a numerical value of 1, and the size of the error was scored according to the following scale: if the subject's error was one position from the correct one, his size of error was one; if it was two positions away it was two; if

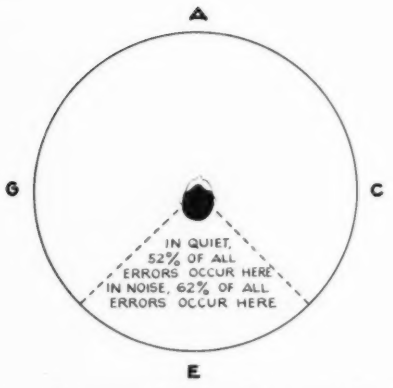


Fig. 3.—Area of greatest difficulty for normal hearing listeners to localize.

	NORMAL	IMPAIRED	NORMAL	IMPAIRED
QUIET	1.05	4.49	2.35	8.99
NOISE	1.35	5.14	2.85	10.3
NUMBER	40	51	40	51

Fig. 4.—Comparison of normal hearing population to monaurally impaired population. Plain bars show error in quiet room; dotted bars show error when noise background was added.

three away it was three, with the maximum size of the error possible equal to four.

RESULTS

Description of Normal Localization Ability. For the entire normal population, the mean number of errors was 1.05 in conditions of quiet, and 1.35 in conditions of noise; the size of the error was 2.35 in quiet and 2.85 in noise. Therefore, the normal population was able to correctly determine the location of 87% of the signals presented them in quiet, and 84% when noise was introduced.

Within the normal hearing population, some variation was evident within the sub-samples. For example, under the more variable condition of quiet, the mean error for females was .6; for males it was .9; for children it was 1.2; and for adults with high frequency loss it was 1.5. Since the primary purpose of determining normal hearing scores was to obtain means for comparison with impaired subjects, these figures were not subjected to statistical analysis. However, it would appear that the variation present is so small as to represent nothing more than random variation.

Of interest, it appeared that the area most difficult for the normal hearing population to localize was the rear area (positions D,E,F). In quiet 52% of all errors occurred here; in noise 62% occurred here.

Comparison of Normal Hearing Population to Monaurally Impaired Population. The mean number of errors for the abnormal population was 4.49 in quiet, and 5.14 in noise; the mean size of the error was 8.99 in quiet and 10.3 in noise. Therefore, as compared to the normal hearing population who could correctly localize 87% of all signals, the abnormal population could correctly localize only 44%. In noise, localization ability appeared to deteriorate further, when the impaired population could correctly localize only 36% of all signals, as compared to 84% for their normal hearing peers. Similarly, in quiet the size of the error for the monaurally impaired population (8.99) was 382% greater than that obtained by the normal hearing population (2.35). Subjecting these means to statistical comparison, using the Fisher t formula for evaluation, yields a t score of 8.8, which indicates that the differences observed are real and are significant at the 1% level of confidence.

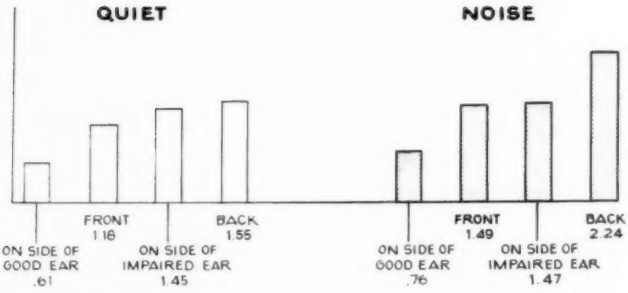


Fig. 5.—Illustrates the variation of ability to localize sound to the side of the good ear, in the front area, on the side of the poor ear, and in the rear (back) area, for size of error.

Areas of Localization Difficulty in Impaired Listeners. In considering the total number and size of the errors occurring, it is of interest to note that the area in which localization ability appeared best, although indeed not perfect, was that area to the side of the better, normal, ear, and difficulty in localization became progressively greater in the front, on the side of the poor ear, and in rear positions. While the actual number of errors does not appear to change significantly in these areas, the size of that error does appear to become correspondingly larger.

Comparison of Males to Females. The mean number of errors made by females was 4.41; for males it was 4.6; the mean size of the error for females was 8.99, for males it was 9.0. Numerically, these are almost identical scores, and by subjecting these scores to statistical comparison, using a Fisher t formula, the obtained t scores ($t = .11$ for number of errors; $t = 0.71$ for size of errors) are insignificant, thus indicating that there are no real differences between the male and female populations in localization difficulty.

Comparison of Impaired Listeners with a Completely Normal Better Ear to Those with High Frequency Loss in the Better Ear. The mean number of errors for the monaurally impaired population with a completely normal better ear was 4.06; for the group with a high frequency loss it was 5.27. The size of the error for the group with

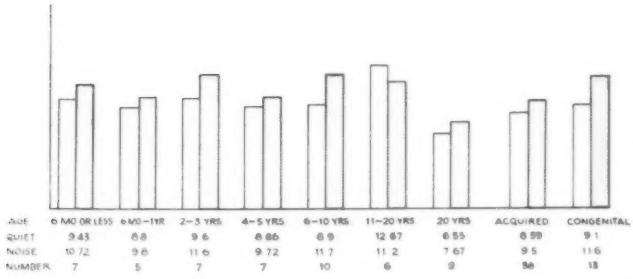


Fig. 6.—Illustrates the size of the error occurring at various duration intervals and, to the right, the size of the error obtained by acquired and congenital problems. Plain bars show error in quiet room; dotted bars show error when noise background was added.

the normal ear was 7.64; for the group with high frequency loss it was 11.43. Since the numerical values obtained between these two groups showed sizable differences, they were compared statistically. Using the Fisher t formula, the obtained t scores ($t = .8$ for number of errors; $t = 1.21$ for size of error) are insignificant. Therefore, it would appear that the presence of a high frequency loss in the better ear does not operate to further deteriorate localization ability in the instance of unilateral impairment.

Comparison of Listeners with Congenital Impairment to Those with Acquired Impairment. The mean number of errors made by those with acquired impairment was 4.1, for those with congenital impairment it was 5.3; the size of the error for the acquired groups was 8.39, for the congenital group it was 9.1. Subjecting these scores to statistical comparison using the Fisher t formula, the obtained t scores ($t = .72$ for number of errors; $t = .22$ for the size of the erors) do not show significant differences. Therefore it would appear that whether a monaural loss is of congenital or acquired origin is an insignificant factor in the resulting localization difficulty, which is essentially the same for each group.

Correlation of Duration of Loss with Difficulty in Localization. In an effort to determine if localization ability improves with time for impaired listeners, a Pearson correlation of the amount of difficulty

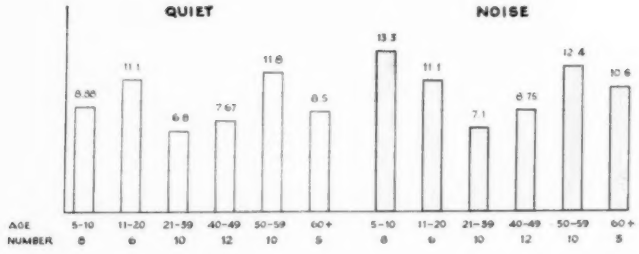
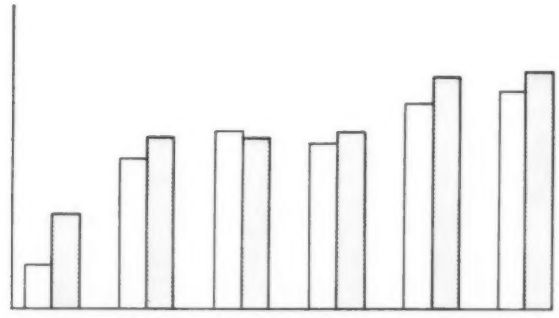


Fig. 7.—The size of the error for various age levels is shown at the top of each bar graph.

and the duration of the existing impairment was obtained. This correlation was obtained for the size of the error only, since this condition seemed to be the more sensitive indicator of variation. The correlations obtained ($r = -.13$ in quiet; $r = -.22$ in noise) appeared to indicate a negative trend, one in which difficulty decreases as duration increases. However, these correlation coefficients were so small as to be statistically insignificant, and therefore, it would appear that the duration of the loss does not influence the resulting localization difficulty.

Relationships of Difficulty in Localization to Age. Monaurally impaired subjects ranged in age from 7 years to 77 years, with a mean age of 38 years. Subjects were grouped into the following sub-sample populations: 5-10 years; 11-20 years; 21-39 years; 40-49 years; 50-59 years; 60 years and above. An analysis of the variance of these group means in quiet ($F = 1.06$) revealed only insignificant chance variation. However, under conditions of noise, the variance present ($F = 2.85$) was significant at a 5% level of confidence, with greater difficulty observed at the extreme age levels (very young - very old) as compared to the young adult and adult populations.

Relationship of Difficulty in Localization to Degree of Impairment. Examination of the individual subject's scores appeared to indicate that, as the degree (amount) of impairment increased, the size and number of the errors occurring correspondingly increased. For example, the percentage of errors occurring in quiet at increasing

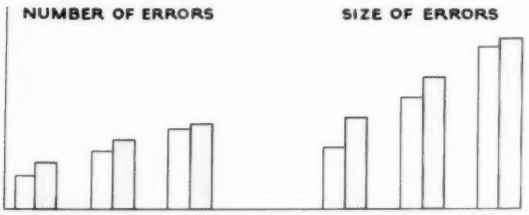


DB	30—39	40—49	50—59	60—69	70—79	80 +
QUIET	2.46	8.75	10.5	9.67	12.2	12.85
NOISE	5.48	10.0	9.98	10.33	13.8	13.9
NUMBER	13	8	8	3	5	14

Fig. 8.—Illustrates the size of the error occurring at various levels of impairment. Plain bars show error in quiet; dotted bars show error when noise was added.

degree levels is as follows: 30-39 db = 24%; 40-49 db = 56%; 50-59 db = 62%; 60-69 db = 62%; 70-79 db = 70%; 80 db + = 76%. Accordingly, a Pearson correlation of the size of the error and the degree of the impairment was made and the obtained correlation coefficients ($r = .58$ for size of error in quiet; $r = .605$ for size of error in noise) are statistically significant at the 1% level of confidence, indicating that these two factors are indeed related, and that as one becomes larger, so does the other. Since the degree group 30-39 db showed a comparatively small size error, this same correlation was performed, removing this degree group. The resultant correlation coefficients ($r = .337$ for size in quiet, $r = .431$ for size in noise) are smaller but nevertheless statistically significant at the 5% and 1% levels of confidence respectively.

Relationship of Difficulty in Localization to Etiology. Monaurally impaired subjects were grouped according to the following etiological categories: otitis media, otosclerosis, other conductives, congential, hydrops, and other perceptives. An analysis of the variance of these group means ($F = 5.92$ for size in quiet; $f = 4.4$ for size in noise) indciates that there is significant variation present at the 1%



TYPE	CONDUCTIVE	MIXED	PERCEPTIVE	CONDUCTIVE	MIXED	PERCEPTIVE
QUIET	2.42	4.17	5.8	4.4	8.08	11.96
NOISE	3.5	4.92	6.2	6.71	9.58	12.08
NUMBER	14	12	25			
DB LEVEL	41.2	49.9	78.48			

Fig. 9.—Illustrates the number and size of errors for various pathological groups. Plain bars show error in quiet; dotted bars show error when noise was added.

level of confidence and that the various etiological groups differ from each other because of factors other than chance.

Relationship of Difficulty to Type of Impairment. Monaurally impaired subjects were grouped according to the following types of impairment: conductive, mixed, and perceptive. Comparatively, conductives had the smallest percentage of errors (30% in quiet, 43% in noise), mixed losses had considerably more (51% in quiet, 61% in noise) and perceptives had the largest percentage of errors (72% in quiet, 77% in noise). Similarly, the size of the error demonstrates a corresponding relationship, where the size of the error for the mixed loss group (8.08) is almost double that for conductives (4.4) while perceptives nearly triple it (11.96). An analysis of the variance among these groups, for size of error only, indicates variance present at the 1% level of confidence ($F = 12.82$ for size in quiet; $F = 11.06$ for size of error in noise). However, it is important to note that, in terms of db of impairment, these three groups have considerable differences (mean conductive loss = 41.2 db; mean mixed loss = 49.9 db; mean perceptive loss = 78.48 db), and since it has been established that greater impairment produces greater localization difficulty, it is difficult to determine whether these differences result from differences in type of pathology or from differences in degree of impairment. In an effort to clarify this question, smaller samples were selec-

ted from these three groups, and extreme degrees of impairment were eliminated, so that the resulting samples had approximately equal degrees of impairment (mean conductive loss = 51.2 db; mean mixed loss = 50 db; mean perceptive loss = 55 db). Even though impairment levels were so controlled, a similar trend appeared both for the number of errors (conductive = 3.2; mixed =4.8; perceptive = 5.8) and for the size of errors (conductive = 7.0; mixed = 9.5; perceptives = 11.5) with conductives doing best, mixed less well, and perceptives least well. Since the numbers within these samples were so small (conductive = 5; mixed = 7; perceptive = 7) statistical comparison could not be made; however, it would appear that this substudy supports an impression that the type of impairment present is a real factor in determining the amount of localization difficulty. It is also interesting to note that within this small sample population, the number of errors did not vary remarkably from type loss to type loss on the side of the poor ear (conductives = 2.0; mixed = 2.0; perceptives = 2.4) but the above noted trend appeared to be present on the side of the good, normal ear (conductive = .5; mixed = 1.6; perceptive = 2.0), which, perhaps, reflects something about the essential pathology present.

SUMMARY AND CONCLUSIONS

A simple test of localization ability was conducted upon forty normal hearing subjects and fifty-one monaurally impaired subjects in the Audiology and Speech Clinic of the University of California Medical Center, San Francisco, California. The results obtained appeared to indicate the following:

1. Normal hearing subjects were able to localize correctly 87% of all test stimuli in quiet and 84% of test stimuli in noise. The area in which normal hearing subjects had most localization difficulty was the rear area.

2. Monaurally impaired subjects demonstrated statistically greater difficulty in locating sound than their normal hearing peers, and as a group, they were able to correctly localize only 44% of all test stimuli in quiet, and 36% when a noise background was introduced. The smallest number of errors was obtained in the area to the side of the good, normal ear, and difficulty in localization became progres-

sively greater in the front, to the side of the impaired ear, and the rear areas.

3. Among monaurally impaired subjects, variations in the amount of difficulty occurring do exist at a statistically significant level. The primary factors which appear to produce significant variations are degree of loss, in which difficulty in localization increases with increasing degree of impairment, and the type of loss present, in which conductives have least difficulty in localizing sound. Mixed losses have statistically greater difficulty, and perceptive losses have greatest localization difficulty. Sex did not appear to be a significant factor nor did age in quiet; however, extreme age groups appear to have greater difficulty localizing sound in noise backgrounds.

4. Subjects whose monaural impairments are of congenital origin have essentially the same difficulty in localizing sound as do those who had normal function and then acquired unilateral impairment.

5. It would appear that the difficulty in localization resulting from the unilateral impairment of auditory function is permanent and does not improve with time.

UNIVERSITY OF CALIFORNIA MEDICAL CENTER

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ANNALS

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GEORGE MORRISON COATES, M.D.

1874 - 1960

George Morrison Coates died suddenly of coronary occlusion at his home in West Whiteland, Chester County, Pennsylvania, on February 7, 1960. He had continued in private practice at his office in Philadelphia and was engaged in his numerous editorial activities until his death occurred within a month of his eighty-sixth birthday.

He occupied a pre-eminent and unique position in otolaryngology for more than sixty years. The weight of his support sufficed to ensure the success of many controversial innovations in the practice and teaching of the speciality. Because of his modesty, kindliness and strict honesty, he was known as "the man without an enemy," and yet, once convinced of the merit of an individual or a cause, he was an inflexible and courageous defender.

Dr. Coates was born in Philadelphia on March 24, 1874. His Quaker ancestors had settled in the Delaware Valley prior to the arrival of William Penn. Two of his ancestors were among the founders and early members of the Board of Managers of the Pennsylvania Hospital, the first hospital to be founded in the United States, and members of his family have been associated with it continuously ever since. His father was variously a cotton broker, textile manufacturer, magazine writer and novelist.

He spent his early years in Berwyn, Chester County, Pennsylvania, and graduated from the Haverford School in 1890, receiving the coveted prize in Greek. From the University of Pennsylvania, he received the degree of Bachelor of Arts in 1894, and the degree of Doctor of Medicine in 1897. During his college years, he was active in sports, acted as captain and manager of the track team and was captain and manager of the football team. As champion bicycle racer, he received numerous cups and trophies. He was on the editorial board and acted as sports reporter of the weekly college paper and, later, was on the editorial board of the Alumni Register, president of the Alumni Society and permanent president of his class.

Dr. Coates served an internship at St. Christopher's Hospital for Children from 1897 to 1898, and at the Pennsylvania Hospital from 1899 to 1901. He began the study of laryngology with Dr.

GEORGE MORRISON COATES

Francis R. Packard at the Pennsylvania Hospital and with Dr. Walter Roberts at the Philadelphia Polyclinic and College for Graduates in Medicine between 1901 and 1905. At the latter institution, he became Associate Professor of Otology, and with its merger with the Graduate School of Medicine of the University of Pennsylvania in 1919, he was appointed Professor and Chief of Service of Otolaryngology in the Graduate School. He was also Professor of Otolaryngology and Chief of Service in the School of Medicine of the University of Pennsylvania from 1933 to 1939, when he became Emeritus Professor. For many years he was Chief of Service at the Presbyterian Hospital, Abington Memorial Hospital, Germantown and Chester County Hospitals.

Dr. Coates was certified by the American Board of Otolaryngology in 1925, becoming a member of the Board in 1930, and later senior consultant. He was a past president of the American Laryngological Association, the American Otological Society, the American Academy of Ophthalmology and Otolaryngology and the Philadelphia Laryngological Society. He was a corresponding fellow of the Societé de Laryngologie des Hôpitaux de Paris and a fellow of the American Bronchoesophagological Association, the College of Physicians of Philadelphia, the American Society of Immunologists, the American College of Surgeons and the Pacific Coast Oto-Ophthalmological Society.

He was chairman of the section of Laryngology, Otology and Rhinology of the American Medical Association in 1927; chairman of the ear, nose and throat section of the Pennsylvania Medical Society in 1921; chairman of the ear, nose and throat section of the Clinical Congress of Surgeons of North America from 1921 to 1936, and chairman of the ear, nose and throat section of the College of Physicians of Philadelphia from 1928 to 1930.

Dr. Coates was editor-in-chief of the A.M.A. Archives of Otolaryngology from 1937 to the time of his death; co-editor with Dr. Chevalier Jackson of "The Nose, Throat and Ear and Their Diseases" (1929); co-editor with Dr. I. S. Ravdin of the American Edition of "Kirschner's Operative Surgery" (1937), and editor of the five volume "Otolaryngology" (1955). He was the recipient of the Newcomb Award of the American Laryngological Association in 1943 and of the deRoaldes Gold Medal in 1949; the Award of Merit of the American Academy of Ophthalmology and Otolaryngology in 1946, and the Gold Medal Award of the American Otological Society in 1949.

As Assistant Surgeon in the United States Navy during the Spanish American War, he participated in the Battle of Santiago Bay.

He served as Lieutenant to Lieutenant Colonel in the Medical Corps of the Pennsylvania National Guard from 1900 to 1916, and as Major to Colonel, MC, U.S. Army, from 1917 to 1919. During World War I, he was chief of the section of head surgery at base hospitals in Camp Sevier, South Carolina, and Camp Hancock, Georgia; commanding officer of Base Hospital No. 56, Allerey, France; otolaryngologist to Embarkation Camp, Bordeaux, France, and president of the Reclassification Board.

Dr. and Mrs. Coates were active in the Episcopal Church. Their home in Philadelphia was a mecca for visiting colleagues from the Americas and Europe and students were always welcomed. Perhaps his greatest interest was the teaching and counselling of young men in the profession. His advice was invaluable because of his exhaustive knowledge of the available teaching programs and of the ability of teaching personnel. Many of the advances in graduate medical education were the result of his unflagging efforts to improve methods of instruction. In addition to his wide interests in military, zoological, geographic, athletic and literary societies, he served as a member of the Executive Committee of the Boy Scouts of America, a member of the Board of Trustees of Haverford School, a trustee of St. Michael's Home for Crippled Colored Children, and a trustee of the Pennsylvania Institute for the Instruction of the Blind.

A daughter, two grandchildren, a brother and two sisters survive.

H.P.S.

FELIX ROBERT NAGER, M.D.

1877 - 1959

On September 7, 1959, there passed from the scene one of the great figures of modern otology. Doctor Felix Robert Nager, who died after a long illness at the age of 81, was honorary professor of otology in the University of Zurich. Professor Nager was one of the last of the pioneers who guided the young specialty through an era of indifference, often amounting to neglect, on the part of the university faculties of that day.

After an assistantship in the Pathological Institute of Zurich he studied under Bezold in Munich and under Siebenmann in Basle. At 31 he returned to the University of Zurich where he began a long and strenuous campaign to lift otolaryngology to the level of recognition to which he felt it was entitled.

Curiously, his early troubles find a counterpart in so many of the difficulties which seem to have beset the young otologists of the early part of this century who attained the highest recognition in their later years. His was the familiar background of remote and inadequate quarters, of instruments personally furnished, of the clinical nurse paid by a voluntary assistant himself unsalaried. It was not until 1918, some ten years after the opening of the polyclinic, that Nager finally managed to obtain adequate quarters in which to carry on his work and in which the pathological and anatomical material was gathered which, even now, is unique in many respects.

Again, as sometimes happens, Professor Nager's scientific attainments were first recognized abroad and his international reputation, which later brought him such recognition as honorary fellowships of the American Otological Society, the American Laryngological Association and the Royal College of Surgeons of England, was only later reflected in his homeland. His earlier papers dealt with a wide variety of subjects but his later interests were almost entirely in the field of otology and the histopathology of the ear, for which he was best known.

In the course of his career he received many honors. In America he was an honorary member of the American Academy of Ophthalmology and Otolaryngology, of the American Laryngological Associ-

FELIX ROBERT NAGER

ation, the American Otological Society and the Harvey Society. He was one of the founders of the Collegium Oto-rhino-laryngologicum and he read the Felix Semon Lecture at the University of London in 1939.

He leaves behind him a heritage of accomplishment and a host of disciples who will long carry on his teachings.

PROF. PIETRANTONI

The Otorhinolaryngological Clinic of the University of Milan announces with sadness the death of Prof. Luigi Pietrantoni in Milan on March 3, 1960.

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